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U.S. DEPARTMENT OF HEALTH
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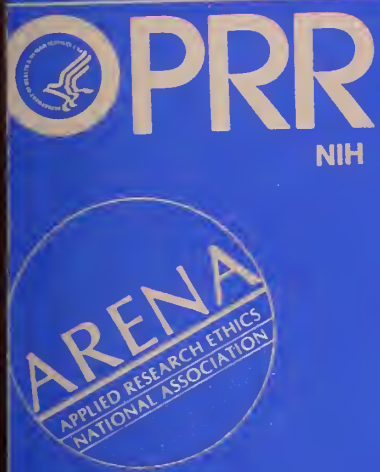

Institutional Animal Care and Use Committee Guidebook

U.S. DEPARTMENT OF HEALTH
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NIH

ARENA
APPLIED RESEARCH ETHICS
NATIONAL ASSOCIATION

Institutional Animal Care and Use Committee Guidebook

Institutional Animal Care and Use Committee Guidebook
Table of Contents

Tables

Foreword

The role of the Institutional Animal Care and Use Committee (IACUC) in ensuring the ethical and sensitive care and use of animals in research is pivotal. The Office for Protection from Research Risks (OPRR) of the National Institutes of Health has made this the cornerstone of its approach to ensuring the highest standards for animal use. Similarly, the Animal and Plant Health Inspection Service of the U.S. Department of Agriculture's approach to regulation underscores this principle. It is with this fundamental premise that the idea and focus of this Guidebook was conceived by the Council of the Applied Research Ethics National Association (ARENA), a national organization for members of IACUCs, Institutional Review Boards, Hospital Ethics Committees, and similar groups concerned with ethical and practical issues related to the conduct of research. With the endorsement and support of its parent body, Public Responsibility in Medicine and Research, ARENA authorized the project and the appointment of an Editorial Board. Distinguished individuals related to the animal care and use field were identified, and accepted the responsibility for the development of *A Guidebook for Institutional Animal Care and Use Committees.*

At the first meeting of the Editorial Board it was agreed that the primary goals of the project would be:

1. To develop a manual for guidance of IACUCs.
2. To incorporate relevant laws and regulations into that manual.
3. To organize this (reference) manual so as to lend itself to being kept current.

Thus, although it was felt that the Guidebook would be helpful to researchers, administrators, and others related to research involving the use of animals, the focus on, and importance of the IACUC member to the process was affirmed.

The many authors, listed on page iv, made this publication possible. The Editorial Board salutes them for their most generous contribution of time, knowledge, and experience. Their quick willingness to take on the responsibility was exemplary; and all users of the Guidebook are their beneficiaries.

The decision of the OPRR to issue this Guidebook to institutions with Animal Care and Use Assurances (paralleling *The Official IRB Guidebook*, which was produced some years ago) is a testament to the Office's basic postulate that control of animal care and use programs should be within the institution carrying on the research. This Office's partnership in the editing, publication, and issuance of the Guidebook has been invaluable, and the informed, hands-on help of the staff of its Division of Animal Welfare has been incalculable.

It is with deep personal feeling, and on behalf of ARENA, that I express appreciation to, and honor the members of the Editorial Board. Their personal investment and untold hours of work made the fruition of this project possible.

David B. Bernhardt, Chairman
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Guidebook

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SPECIAL CONSIDERATIONS | RESOURCES | ANIMAL CARE AND USE COMMITTEE (IACUC) | REVIEW OF PROPOSALS | OVERSIGHT OF ANIMAL CARE AND USE PROGRAMS | EVALUATION OF ANIMAL WELFARE CONCERNS | RECORD KEEPING AND REPORTING

A.
The Institutional Animal Care and Use Committee (IACUC)

A-1.
Background and History

Introduction

Historically, regulations concerning the care and use of animals in laboratory research have been derived from two main sources: the experimental scientists themselves and the local humane societies formed to protect pets, farm animals and work animals from abuse. Since 1896, when the National Institutes of Health (NIH) originated, it has taken an active role in encouraging proper care and use of laboratory animals.

In the 1920s, the Director of NIH held himself personally responsible for decisions on the use of animals in any given experiment and whether the requirement for anesthesia could be waived. During the Second World War, the Committee for Medical Research was created by Franklin D. Roosevelt and, in conjunction with the National Research Council of the National Academy of Sciences, it mounted a major effort to reduce the effects of war-related disease and injury. In 1946, fifty projects from the Wartime Office of Scientific Research were transferred to NIH and the budget for the latter increased, from $180,000 in 1945 to $8,000,000 in 1947. In 1958, NIH's Division of Research Grants was reorganized and the peer review system for selecting the most meritorious grant applications was developed.

In 1963, the first edition of the *Guide for the Care and Use of Laboratory Animals (Guide)* was issued by the Animal Care Panel (later renamed the American Association for Laboratory Animal Science). Subsequent editions of the *Guide* have been developed by the National Research Council (NRC). The fifth, and most recent, edition of the *Guide* was published in 1985 (NIH85-23, later numbered NIH86-23). This is the primary reference for research animal care and use in the United States.

In 1966, suggestions in the press that pets were being used in research caused a public outcry and led to Congress' enacting the Pet Protection Act of 1966, the first version of what is now called the Animal Welfare Act (AWA). The United States Department of Agriculture (USDA) was given responsibility for implementing the new law. The act applied only to dogs, cats, rabbits, monkeys, guinea pigs and hamsters. Although research facilities were required to be registered, to have their suppliers licensed, and to undergo inspection by Animal and Plant Health Inspection Service (APHIS) personnel, the Act did not apply directly to the conduct of research using animals. The AWA was revised in 1970 and 1976, and underwent a major revision in December 1985. Although NIH is not responsible for enforcing the Act, requirements for compliance with it have been incorporated into any research conducted or supported by any component of the Public Health Service.

In 1973, a new policy applying to all PHS awardee institutions was drafted. This PHS Policy required compliance with AWA and the recommendations of the *Guide.* It also required each institution to provide NIH with an assurance which gave a detailed plan for research, training, testing, education, experimentation, or demonstration purposes. An institution's failure to comply could lead to withdrawal of NIH approval and suspension or termination of all PHS-supported research at that institution. Individual investigators could be disqualified from receiving PHS awards. Thus, this Policy required that individual institutions assume responsibility for the quality of its animal research program and the conduct of its investigators and animal care personnel. However, the very general nature of the PHS Policy made its enforcement difficult.

In 1974, the Institutional Regulations Branch of the Division of Research Grants was transferred to the Office of the Director of NIH and renamed the Office for Protection from Research Risks (OPRR). The third PHS Policy was prepared jointly by OPRR and what is now called the National Center for Research Resources, and came into effect January 1979. It covered all vertebrates used in research and the emphasis was put on the responsibility of awardee institutions to train staff for the management of their animal programs. This Policy gave institutions three options for obtaining NIH approvals: 1) accreditation by the American Association for Accreditation of Laboratory Animal Care (AAALAC); 2) an assurance that the institution's own Animal Care Committee had found the institution in full compliance with the *Guide;* and 3) provisional assurance of plans for correction, if deficiencies found by the Committee's annual inspection were reported to OPRR.

In July 1981, NIH issued the first comprehensive Policy which required written assurance of accreditation, either by an appropriate professional body, or by an institutional committee which included at least one veterinarian, before NIH funding could be awarded for research or teaching. The standards for evaluation were those set forward in the *Guide,* with annual institutional committee inspections.

During the 1980s the incidents of vandalism, harassment and thefts of animals increased substantially. Subsequently, Congress has manifested an increasing interest in the care and use of laboratory animals, and powerful lobbying forces have maintained this interest. A new committee was formed to revise and update the PHS Policy, concurrently with the Institute for Laboratory Animal Research of the National Academy of Sciences being commissioned to update the *Guide.* The final version of the PHS Policy, THE PUBLIC HEALTH SERVICE POLICY ON HUMANE CARE AND USE OF LABORATORY ANIMALS, was made effective January 1, 1986. It extends to foreign institutions receiving PHS funding and to intramural institutions operated directly by NIH and other agencies of PHS. The process of revision of the Policy was closely followed by Congress. Subsequent to the revision, Congress enacted the Health Research Extension Act, which added several provisions to PHS Policy. The latter was revised to conform with the new law and reissued in September 1986. Key elements of PHS Policy include:

1. Negotiation of Animal Welfare Assurances which include commitments by the awardee Institution to its animal care and use program, to appropriate staff training, and to an occupational health program for employees;

2. establishment, according to specified criteria, of an Institutional Animal Care and Use Committee with defined responsibilities;

3. detailed requirements for the submission of applications for awards;

4. recordkeeping requirements to ensure clear accountability for the quality of the program; and

5. reporting requirements to enable funding agencies and OPRR to exercise oversight of the entire system.

Each institution subject to the PHS Policy is expected to operate its program in accordance with the U.S. Government Principles for the Utilization and Care of Vertebrate Animals used in Research and Training. Recently, the USDA issued Parts 1 and 2 of final regulations implementing the 1985 amendments to the AWA. Part 2, subpart C pertains to research institutions. Most of the provisions included in this subpart of the USDA Regulations are similar or identical to those included in the PHS Policy. Part 3 of the implementing USDA Regulations describes the standards which must be met when using species of animals covered by the USDA Regulations. Many of the requirements specified in Part 3 are similar to the recommendations made in the *Guide* and establish standards for the care and maintenance of covered species.

A-2. Authority, Composition and Functions (See Table 1)

Each institution which falls under authority of the AWA and/or receives PHS support for research and teaching involving laboratory animals must operate a program with clear lines of authority and responsibility, a properly functioning Institutional Animal Care and Use Committee (IACUC), procedures for self monitoring, adequate veterinary care, a program of occupational health, sound animal husbandry practices, and appropriate maintenance of facilities for housing animals.

The IACUC also monitors the use of animals in teaching activities as specified in the USDA Regulations, but this does not come under the Policy, unless it is supported by PHS.

The IACUC must have at least five members, including a veterinarian with program responsibilities, a scientist experienced in laboratory animal research, a non-scientist and an individual who has no other affiliation with the Institution besides membership in the IACUC. The IACUC must have the full support of the Institutional Official responsible for the program; evaluate the entire program every six months; prepare a report on the evaluation and the inspection of the facilities which is to be filed with the Institutional Official; and make recommendations to this Official concerning deficiencies, with a proposed timetable for corrections. The IACUC has the authority to suspend PHS-supported research activities.

The IACUC has an obligation to review all research projects, proposed for PHS support, prior to their receiving funding. A written report of this review confirms that the project will be conducted in accordance with PHS Policy, the *Guide* and the AWA. At least one member of the Committee must review each proposal, but all members must have prior opportunity to

request full Committee review. The IACUC has authority to approve, require modifications before approval, or withhold approval of proposals submitted to it for review. No activity involving animals can begin unless it is first approved by the IACUC.

The frequency of IACUC consideration of approved, ongoing activities is one of the few areas in which PHS and USDA have differing requirements, i.e., PHS requires it at least once every three years, whereas USDA requires it annually. Ideally, institutions should choose to establish a uniform mechanism which satisfies both federal requirements. In deliberating this issue it is helpful to refer to consideration of ongoing activities by the use of the term "annual review" as opposed to the function of the IACUC performed at the outset of a new activity and at the expiration of an approved activity, referred to as "review." OPRR has interpreted PHS Policy to require an institutional process which provides review of proposed activities, with committee approval for a specified period of time generally not to exceed three years. This **"initial renewal review"** and approval may be accomplished by either convened Committee action or by a "designated reviewer/expedited review" process which meets the PHS Policy requirements of Section IV.C.2. During this period of approval, annual review must be accomplished to meet USDA requirements. The purpose of **annual review** is to confirm that no changes have taken place in the approved activity which might require further **consideration** by the IACUC, and to ensure that any new requirements of PHS, USDA or the institution are transmitted to the investigator. **Annual review** need not require a convened IACUC or designated reviewer/expedited action but must be adequately documented. Planned modifications must be brought to the attention of the IACUC prior to initiation. A relatively simple mechanism to meet USDA requirements is the annual circulation of a standard form giving current basic IACUC information, e.g., approval number, date, title, species, etc., to all investigators with IACUC-approved activities. The investigator then notes that either no changes have taken place, or he/she describes any changes which have occurred. The IACUC may then separate responses, filing those indicating no changes and passing along the remainder to an IACUC-designee for assessment of the changes reported. Any changes to the approved activity which are deemed of sufficient magnitude to merit further consideration may then be presented to the IACUC. All of these dispositions should be documented as official IACUC actions.

Table 1
Federally Mandated IACUC Functions

1. Review, at least once every 6 months, the research facility's program, using USDA Regulations/*Guide* as basis.

2. Inspect, at least once every 6 months, all of the animal facilities, including animal study areas/satellite facilities, using USDA Regulations/*Guide* as basis.

3. Prepare reports of IACUC evaluations and submit the reports to the Institutional Official.

4. Review and investigate legitimate concerns involving the care and use of animals at the research facility resulting from public complaints and from reports of non-compliance received from facility personnel or employees.

5. Make recommendations to the Institutional Official regarding any aspect of the research facility's animal program, facilities or personnel training.

6. Review and approve, require modifications in (to secure approval), or withhold approval of those components of proposed activities related to the care and use of animals.

7. Review and approve, require modifications in (to secure approval), or withhold approval of proposed significant changes regarding the care and use of animals in ongoing activities.

8. Suspend an activity involving animals when necessary; take corrective action and report to funding agency and USDA.

B.
IACUC Review of Proposals

B-1.
Fundamental Issues, Criteria (See Table 2)

Introduction

Current federal regulatory policy, as well as generally accepted ethical principles, incorporate two general goals. The first is that scientific reliance on live animals should be minimized. The second is that pain, distress, and other harm to laboratory animals should be reduced to the minimum necessary to obtain valid scientific data. Federal policy directs the IACUC to review proposals for animal use to ensure that investigators incorporate these principles into their research.

Reducing and avoiding animal use

The number of experimental animals should be the minimum necessary to produce valid results. When possible and appropriate, a non-animal substitute should be used, or a species of lower phylogenetic order substituted if available. Unnecessarily duplicative research should be avoided for scientific and ethical reasons.

The level of IACUC involvement in overseeing this process is not clear cut. The decision to require the modification of proposals to take these considerations into account requires an assessment of the necessity of a given procedure. This can be a decision for which the IACUC is inadequately equipped insofar as the Committee cannot expect to cover all aspects of scientific and technical expertise for all proposals which they will be asked to review. However, certain general questions should be answered in the proposal; the onus should be on the investigators to justify and explain their experiments.

While neither PHS Policy nor USDA Regulations explicitly prescribe an institutional mechanism to "track" animal usage by investigators under IACUC-approved activities, both require that investigators include in their applications to the IACUC, identification of the appropriate number of animals to be used, and a rationale for the appropriateness of the species and number of animals they propose to use. These provisions implicitly require that institutions establish mechanisms to monitor and document the number of animals acquired and used in approved activities. OPRR is aware of many institutions at which this mechanism precludes an investigator from using a single animal in excess of the number approved by the IACUC. Other institutions have reported mechanisms by which the number of animals acquired under an approved activity may exceed the approved number by a small percentage, e.g., 5% (this generally applies only to rodents). These institutions require investigators using non-rodent mammalian species to acquire and use only the precise number of animals approved by the IACUC.

Administrative linkage of acquisition of animals to an IACUC approval number is the method of choice employed by many institutions to "track" the number of animals being acquired under an approved activity. Many also have relatively simple computerized systems which will alert the system operator and generate a report when an investigator has reached a preset percentage, e.g., 80-90%, of the number of animals approved for the activity. This report is then submitted to the investigator with a request for specific justification for acquisition of animals in excess of the number approved. Such systems often generate animal identification or cage card labels which provide a simple mechanism to meet the required project-specific assignment of animals to corresponding approved activities. Small institutions using limited numbers of animals may choose to maintain a "hard copy" log of each IACUC-approved activity, merely subtracting the number of animals acquired with each order from the number approved, with verbal notification of the investigator as the number of animals approved is approached. Whatever mechanism an institution chooses, it must satisfy PHS Policy requirement that the use of animals be limited to the minimum necessary to obtain valid results.

Any of the above mechanisms is satisfactory in meeting the requirements of PHS Policy, the *Guide* and USDA Regulations.

Minimizing pain and distress (see also Section B-2-1)

Minimizing pain and distress is a basic aim of the Animal Welfare Act and the PHS Policy. This entails defining, recognizing, and reducing or eliminating these states wherever possible. The inherently

subjective nature of pain makes definition difficult, but several have been proposed. For example, the International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." The American Veterinary Medical Association's Panel report on the Colloquium on Recognition and Alleviation of Animal Pain and Distress has also formulated working definitions of pain, anxiety, fear, stress, distress, comfort, discomfort and injury. These definitions provide useful references for IACUCs.

Human observers must be able to recognize pain and distress in order to minimize them when they occur. While this may be difficult, observable signs may include departures from normal behavior, or appearance and physiological parameters of a particular species or individual animal. The institution, through the IACUC, must ensure that research personnel are appropriately educated on how to assess pain and distress in their laboratory animals. This is particularly crucial for chronic experiments.

Finally, minimizing pain and distress means adopting approaches to eliminate or reduce these states when they are observed. The IACUC must develop familiarity with the most relevant of these strategies and ensure that investigators are educated in the measures applicable to their proposals. The IACUC may prohibit certain procedures altogether if it feels that pain and distress cannot be reduced to an acceptable level.

Evaluating the justification for laboratory animal use

When the IACUC reviews animal use proposals, justification questions will often arise. The need for a given number of animals is probably the most common. Certain proposals will necessarily entail pain and distress, despite all measures taken for their minimization, if the scientific question being asked is to be answered. If there is no alternative to the use of the specified animals, an evaluation of the research must be attempted. The higher the level of the anticipated distress the stronger must be the justification of the value of the research.

Often the IACUC will lack the scientific expertise to perform the relevant evaluation. Also, considerations of social value will be difficult when society itself has not made such determinations. This limits the IACUC's ability to make absolute judgments, but the committee can still have a valuable impact by simply raising the consciousness of investigators to the need for careful preparation of the justifications they supply. If justifications supplied are too general, or in insufficient detail, further elaboration should be sought by the IACUC. Ad--ditional literature reviews describing the potential contribution of the work in terms comprehensible to nonscientist members of the IACUC can also be requested.

The IACUC is usually able to judge the adequacy of the training and skill of the investigators proposing the research. Information on the adequacy of the equipment and facilities should also be made available. Supplemental committee members can be appointed to evaluate specific aspects of proposals submitted to the IACUC, for example, a biostatistician will often be useful either as a consultant or as a full member.

Although certain aspects of proposal review are likely to remain difficult, due to their conceptual complexity and controversial political nature, IACUC members can still do a great deal to ensure that animal research is conducted humanely and ethically in their institution.

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B-1-1. Approval and Disapproval of Proposals

Processing by the IACUC

Most IACUCs require submission of proposals in a particular format, often reflecting requirements of the Animal Welfare Act or other federal regulations. Clear presentation of a proposal will obviously assist the Committee in its deliberations. Also, preliminary discussion between the investigators and Committee members can help the former develop a proposal containing all the requisite information. Often it is helpful for a specific Committee member to be assigned a given proposal for in-depth review and liaison with the investigator. This primary reviewer is responsible for communication with the investigator and for obtaining and relaying information to and from him/her.

Another factor affecting the IACUC response is its technical expertise in areas relevant to the proposal, particularly for very complicated and involved submissions. In some instances the committee may use additional consultants to assist with specific proposals.

As a result of their review, an IACUC may approve a proposal as submitted, may require modification, or may reject a proposal outright.

Unqualified approval: The IACUC considers that all significant points have been addressed by the investigator and that no question has been raised by any elements of the proposed study. As a result of this approval, the investigator has permission to conduct the experiments on the number of animals described in the proposal.

Deferral: This may reflect insufficient information for the IACUC to make a judgment. Absence of Committee members or other procedural reasons make it appropriate to defer a decision.

Approval pending clarification: The proposal may have no major problems but require clarification on specified minor points, signatures of responsible investigators or other administrative paperwork. The approval will be issued when the information is supplied without necessity of further discussion by the full Committee.

Qualified or conditional approval: In these cases the concerns are not major but the IACUC considers specified areas of the proposal inappropriate or problematic. The changes sought may, for example, require the substitution of different drugs or documentation demonstrating that the personnel are appropriately qualified. The approval could also be conditional on further information's being provided, such as preliminary data or substantiating references from the published literature.

Limited approval: This is issued when the IACUC has more serious concerns and feels the need to follow the study more closely. This could be due to complexity of the study or the fact that it entails new and untried procedures. Thus, approval may be granted for preliminary studies with only a limited number of animals. The initial data will then be reviewed by the Committee and the remainder of the proposal decided upon. In these instances, it is important to remember that the primary concern of the Committee is to facilitate the performance of appropriate and productive scientific endeavor, consistent with applicable laws, regulations and policies.

Disapproval: This is rare due to the on-going discussions which usually occur between investigators and Committee members. However, if the investigators refuse to modify their proposal or fail to supply information showing that their laboratory has appropriate facilities, or their staff the necessary training to cover the concerns of the Committee, this may be the only option. A more usual result is withdrawal of the proposal.

Appeal of Committee disapproval

Most committees have procedures for addressing the situation of an investigator who chooses to resubmit a proposal which has been previously disapproved. The appeal should include the provision of additional evidence by the investigator or the solicitation of experts able to assist the Committee in their concerns. In all cases in which there is lack of Committee unanimity, the reasons for disapproval by the majority or minority membership should be presented to the investigator in writing. The Committee records should reflect this diversity of opinion.

Ultimately, the IACUC must take responsibility for using animals in the research conducted at its institution. The disapproved proposals cannot be administratively approved by a higher authority. However, the opposite is not true; an IACUC approved proposal can be administratively disapproved due to financial, facility-related or other considerations.

B-2. Special Issues

B-2-1. Minimization of Pain and Distress

Definitions

For purposes of this discussion, the terms analgesia and anesthesia are defined as follows: **analgesia** is a state of insensibility to pain without loss of consciousness; **anesthesia** is a state of lack of awareness or sensitivity, with or without loss of consciousness. In research using laboratory animals, the appropriate use of anesthetic and analgesic reagents is very important for both ethical and regulatory reasons. Tranquilizers or sedatives may also be used to alleviate distress.

Assessment

All aspects of a proposed study must be thoroughly examined to determine what manipulations may cause pain or distress in the animals to be used. A judgment of the level of pain and discomfort must be made, in conjunction with an assessment of any alternative methods for obtaining the data of interest. Should there be no adequate alternatives, the investigator must decide what reagents can be used to reduce, or eliminate pain and distress. This will include means to assess the effectiveness of the agents and the use of established criteria for re-dosing the animal. The main difficulty is an accurate assessment of pain and distress in an animal.

Table 2
Federal Criteria for Granting IACUC Approval

Activities	Must be in accord with USDA Regulations/PHS Policy.
Pain/Distress	Must avoid/minimize discomfort/distress/pain. If pain/distress is caused, appropriate sedation, analgesia or anesthesia will be used. Attending veterinarian must be involved in planning. Use of paralytics without anesthesia is prohibited. Animals with chronic/severe unrelievable pain will be painlessly killed.
Surgery	Must meet requirements for sterile surgery and pre/post operative care. Cannot use one animal for several major operative procedures from which it will recover, without meeting specified conditions.
Euthanasia	Euthanasia method must be consistent with USDA Regulations/AVMA recommendations.
Housing/Health	Animal living conditions must be consistent with standards of housing, feeding and care directed by veterinarian, or scientist with appropriate expertise.
Alternatives	There must be considered alternatives to painful procedures; also must document consideration of alternatives if animals experience pain or suffering.
Rationale and Methods	Must provide written narrative of methods/sources.
Duplication	Must provide assurance that activities do not unnecessarily duplicate previous efforts.
Qualifications	Personnel must be appropriately qualified.
Deviations from Requirements	Must be justified for scientific reasons, in writing.

Pain is usually defined in terms of human perception of noxious stimuli and the threshold is variable among humans. Animals react similarly to the prick of a needle or the cut of a scalpel, but there is no way to know precisely how and to what degree they perceive such stimuli without imposing human standards upon the process.

Distress is even more difficult to assess. There are no generally accepted criteria for distress, although there are a number of metabolic, physiologic and behavioral parameters which are thought to be altered by it. These include changes in reproductive performance, elevation in glucocorticoid levels, and elevation in catecholamine levels.

Some experimental conditions such as prolonged restraint, alterations in the environmental temperature without provisions for behavioral or physiological adaptations, prolonged food and water deprivation, as well as other procedures whose harshness or duration could be perceived by any organism as perilous, may be assumed to cause distress. While almost any condition can be perceived to cause distress, only those whose magnitude or duration are severe enough to produce significant quantifiable changes should be considered for pharmacologic intervention, providing the use of drugs does not negate the purpose of the experiment. Despite the difficulty, an investigator must attempt to incorporate some objective assessment of the level of discomfort or distress produced.

Choosing an anesthetic or analgesic

The responses of different species to different anesthetics, analgesics or tranquilizers vary and are not fully defined. Often the effects of a given drug have only been examined in a single species and definitive information, for example, on cardiovascular and respiratory function or on the ability to relieve the perception of noxious stimuli, is missing. As a result, dosages have been developed on the basis of the amount required to produce cessation of movement when the animal is confronted by what is assumed to be a painful manipulation, in conjunction with an adequate recovery. Because of the imprecise nature of the studies, dosage ranges are often quite wide, requiring a very conservative approach to their use. The use of drug mixtures further complicates the choice of an adequate dose. Numerous reference texts exist and IACUCs may request their veterinarian to prepare current charts of recommended doses as an institutional resource for investigators.

Summary

While the use of anesthetics and analgesics is far from simple, careful consideration to their use must be given by IACUCs and investigators. In some instances pilot studies may be necessary to assess the compatibility of drugs with the particular investigation proposed. Particularly careful justification must be required of any procedures for which alleviation of pain or distress cannot be reasonably assured. It is the responsibility of the investigator to justify the proposed study and to show that he/she has considered all the options for minimizing pain and distress.

References

AVMA Colloquium on Recognition and Alleviation of Animal Pain and Distress. November 15, 1987. JAVMA, 191(10).

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B-2-2. Surgery

Introduction

Surgery on animals is commonplace in biomedical research. It is a complex issue for IACUCs to address and for institutional veterinarians to monitor. The issue is further complicated by the multiple regulatory requirements, including qualifications of personnel performing the surgery, species-specific facility and anesthetic requirements, requirements for postoperative care depending on species and operative procedure, varying requirements for major and minor surgery, and survival and non-survival procedures.

Surgery and postoperative care are addressed in the *Guide*, PHS Policy and USDA Regulations. These regulatory documents form the basis on which the IACUC must operate. The regulations and guidelines in the *Guide* and USDA Regulations are the most stringent requirements and form the basis for this discussion. Some procedures are banned or discouraged by these regulations. For example, multiple major surgical procedures may not be performed on the same animal for cost considerations, but may be performed if it is a scientifically necessary part of the proposal, has been approved by the IACUC, or if it is necessary for the health of the animal; paralytic agents may not be used without analgesia.

Facilities

The *Guide* provides the most stringent guidelines for surgical facilities. Aseptic facilities for non-rodent mammals should include the following: a surgical support area; a preparation area; an operating room(s); a dressing area for surgeons; and an area for animal intensive care and supportive treatment. The PHS and the AAALAC have interpreted these recommendations to mean a minimum of three rooms; an operating room used solely for that purpose, an animal preparation room and a surgeons' preparation room. The surgical support area for storage and cleaning of instruments and supplies may be combined with another area. Operating rooms should not include sinks and should contain only movable equipment such as anesthetic machines and monitoring equipment. Room surfaces should be impervious to moisture and sanitizable. If volatile anesthetics are utilized, a gas scavenging system should be provided.

With the approval of the IACUC, minor surgical procedures on non-rodent mammals may be performed without the use of a fully aseptic facility. These have been defined as procedures which do not invade a body cavity or produce permanent physiological or physical impairment. Such procedures must still be performed utilizing aseptic technique in accordance with standard veterinary procedures.

Separate facilities are not necessary for rodent surgery, and it may be performed in a laboratory or portion of a laboratory which has been sanitized and provided for that purpose. Non-survival surgery may also be performed in common laboratories. This is defined as surgery in which the animal is not allowed to recover from anesthesia.

Aseptic technique

The use of appropriate facilities must be accompanied by proper techniques to ensure the maintenance of asepsis. This includes the preparation of animals, surgeons, operating rooms, instruments and supplies, and the maintenance of asepsis during the procedures. The requirements for non-rodent mammals are more stringent than for rodents. However, adherence to aseptic techniques is required for all survival surgery regardless of species.

Intra-operative monitoring

An anesthetic proposal appropriate for the species and the procedure forms part of the submission to the IACUC. It must include the methods to be used to maintain an appropriate plane of anesthesia. Monitoring will depend on the procedure but may include body temperature, heart rate, blood pressure, blood gases and electrocardiographic activity. The personnel must be suitably qualified to cope with anesthetic and surgical complications.

For major surgical procedures on non-rodent mammals an intra-operative anesthetic monitoring record should be kept, and included with the surgeon's report as part of the animal's records. This record should be available to the personnel providing postoperative care. Some institutions provide a centralized surgical facility which is staffed by appropriately trained veterinarians and technical staff. While costly, this is probably the ideal method for ensuring that surgical complications are minimized and all regulatory requirements are met.

Postoperative care

The surgeon is responsible for ensuring that care is provided which is both appropriate to the species and to the procedure performed. The institutional veterinarian must oversee the postoperative care programs, but does not necessarily provide care unless complications arise, or his/her consultation is sought.

Components of a postoperative care program include appropriate analgesia, monitoring of surgical wounds, observation of animals for normal behavior, monitoring physiological function and recordkeeping. Special facilities may be required, depending on the procedures performed. For example, complex cardiac surgery may require the use of cages equipped with heat and oxygen, ventilation equipment, and cardiac and blood gas monitoring equipment. Other procedures may need only a technician to observe that the animal has recovered from anesthesia. Supportive fluids, analgesics and other drugs must be provided as needed. An external heat source should be available since animals often become hypothermic while under anesthesia. Postoperative records should reflect that the animal was observed until it was extubated and had recovered the ability to stand.

The postoperative period is generally considered at an end when the skin sutures are removed or the wound has healed. Until this point a minimum of recorded daily observations is needed. Consultation with a veterinarian is encouraged to ensure that adequate analgesia is provided, if necessary, throughout the postoperative period.

Personnel qualifications

The IACUC must decide whether the personnel proposing and supporting surgical proposals are adequately qualified to conduct a given procedure; and if not, how

to ensure adequate instruction. In general, individuals without formal surgical training may perform surgery when qualified by experience. Various requirements may be made as to the professional background of the investigator, and documentation showing ability to perform the specific surgery may be required. Physicians trained in a surgical specialty are expected to be qualified to perform surgery on animals within the same area of surgical expertise they hold as physicians. The same assumption can be made for individuals with dental and veterinary degrees. All other types of surgery will probably require additional, albeit not necessarily formal, instruction. Performing a pilot study under the supervision of an experienced person or as part of a multidisciplinary team should be sufficient. Persons with other graduate degrees, students or technicians, should only perform surgery after formal instruction in surgical techniques or with specific documentation that the proposed technique has been previously performed without complications by the person.

It is impossible to design a standard surgical instruction course which is applicable to all situations. USDA Regulations require that each institution provide instruction in aseptic surgery applicable to their research programs. As a general rule, these courses should include instruction in aseptic technique, anesthesia and analgesia, and proper surgical technique, and may focus on a specific procedure. Cooperative multidisciplinary approaches to the instruction and conduct of the surgery are encouraged.

References

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White, W. J. and K. J. Field. 1987. Anesthesia and surgery of laboratory animals. Veterinary Clinics of North America: Small Animal Practice, 17:989-1017.

B-2-3. Euthanasia

Introduction

PHS Policy and USDA Regulations require that an IACUC review and approve the methods of euthanasia which are proposed. These must be consistent with the recommendations of the 1986 Report of the AVMA Panel on Euthanasia, or succeeding revised editions, unless there are scientific justifications for alternative methods.

Definition

Euthanasia means the humane killing of an animal accomplished by a method which produces rapid unconsciousness and subsequent death without evidence of pain or distress, or a method which utilizes anesthesia produced by an agent that causes painless loss of consciousness and subsequent death. Other criteria used to evaluate the appropriateness of a given method include compatibility with the requirements of the research, reliability, irreversibility, the minimization of distress to animals and persons performing euthanasia, and safety to the latter. The species of animal being used and the qualifications of the investigators are also important considerations.

Methods

Three categories of methods exist: inhalant and non-inhalant pharmacologic agents, and physical methods.

Inhalant Agents:

Carbon Dioxide (CO_2): Carbon dioxide is an effective and widely used agent to euthanize rodents. This method does not cause asphyxiation; depressant and anesthetic activity occur prior to death. Since the effects of carbon dioxide are reversible it is important to ensure that the animals are dead. This can be done by performing a thoracotomy prior to discarding the carcass. Commercially filled tanks of carbon dioxide are the preferred source for CO_2, although with appropriate precautions against possible contact by the animals, dry ice may be used to generate the gas.

Inhalant anesthetics: Halothane, methoxyflurane and isoflurane are often used for small numbers of rodents but their expense precludes their use for larger numbers. As with carbon dioxide, death of the animal must be ensured. It is important to minimize exposure of personnel to these potentially toxic agents; therefore fume hoods must be used. Ether was formerly used extensively but its use is now discouraged because it is a fire hazard and potentially explosive. Similarly, the use of chloroform is discouraged as it is a potential human carcinogen.

Non-inhalant agents:

Barbiturates: These can be used to euthanize virtually any species, but are most commonly used for non-rodents, as equally humane and less time-consuming methods are available for the latter. Most commonly, the barbiturate pentobarbital is administered by intravenous injection. With a dose of twice

that required for anesthesia, unconsciousness occurs in several seconds, followed by death. In animals which are difficult to restrain, a sedative or tranquilizer may be given prior to the barbiturate. Also, the barbiturate can be administered by intraperitoneal injection, but this requires a larger and more variable dose.

T-61: This is a commercial product which has been withdrawn and should no longer be used.

Potassium Chloride (KCl): KCl induces immediate cardiac arrest without any significant depression of the central nervous system. Hence, it must be used only after the animal is deeply anesthetized.

Paralytic agents (succinyl choline, curare, etc.): These drugs induce muscular paralysis and death by suffocation. They have no direct effect on the central nervous system and they must be used only on unconscious animals.

Physical methods:
Physical methods are sometimes necessary to obtain scientifically valid data and, while aesthetically displeasing to some individuals, are entirely humane when administered under controlled conditions.

Stunning: Stunning of rodents and rabbits is accomplished by a blow to the skull of sufficient force to induce immediate unconsciousness. This is followed by decapitation or thoracotomy, with severance of a major blood vessel, to ensure death. An IACUC must be assured that only well-qualified personnel will perform this technique.

Captive Bolt Pistol: This method is used for ruminants and swine when chemical agents are scientifically contraindicated. Penetrating captive bolt pistols are more effective for inducing unconsciousness than non-penetrating pistols and should be used. To ensure death, animals should be exsanguinated subsequent to stunning.

Cervical Dislocation: This is frequently used for mice, birds, immature rats and rabbits weighing less than one kilogram. It is assumed that cervical dislocation induces immediate unconsciousness but it is preferable to sedate or lightly anesthetize the animals first. This method can also be used for hamsters and guinea pigs but is more difficult in these species, due to their muscular necks. The IACUC must be assured that the personnel are appropriately qualified in the use of this method for the specific species involved.

Decapitation: A guillotine may be used to decapitate rodents and occasionally larger species. The section should be through the atlanto-occipital joint. The 1986 AVMA Report recommended that decapitation not be done on conscious animals until further information became available. A 1988 report concluded that appropriately performed decapitation of conscious animals does not produce neurological evidence of pain or distress. This additional information may be taken into account by IACUCs, while alternative methods should always be considered.

Microwave irradiation: This method is used when a project requires fixation of brain metabolites without the loss of the anatomic integrity of the brain. Commercial microwave chambers are available for rodents which will render an animal unconscious in less than a second. These instruments differ from household units in that they direct most of the rays at the head. The kilowattage needed to induce immediate unconsciousness is proportional to the animal's size.

Exsanguination: This must not be performed on conscious animals.

Euthanasia of poikilothermic animals

The 1986 Report of the AVMA Panel on Euthanasia does not address poikilothermic animals beyond stating that methods for mammals may be inappropriate. Two useful guides for euthanasia of such species are Humane Killing of Laboratory Animals and the Canadian *Guide for the Care and Use of Experimental Animals.*

Chemical Agents
Intraperitoneal administration of pentobarbital is an effective method of euthanasia in amphibians, turtles and snakes. Tricaine methane sulphonate (MS222), commonly used to anesthetize frogs and toads, may be used for euthanasia. Inhalant anesthetics such as halothane may be used for amphibians and reptiles. Due to the low oxygen requirements for reptiles, the onset of unconsciousness and death will be significantly lengthened.

Physical Methods
Frogs and toads may be euthanized by stunning or pithing. Turtles may be euthanized by stunning. Decapitation is not humane due to the long period needed to induce unconsciousness by hypoxia.

References

Humane Killing of Laboratory Animals, 4th Edition. 1988. Universities Federation for Animal Welfare, Potters Bar, Herts, England.

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Vanderwolf, C. H., G. Buszsaki, D. P. Cain, and B. Robertson. 1988. Neocortical and hippocampal electrical activity following decapitation in the rat. Brain Research 451:340-344.

Guide to the Care and Use of Experimental Animals. 1980 and 1984. Canadian Council on Animal Care. Vols. 1 and 2.

B-2-4. Methodology

Animal preparation

All animals should exhibit normal behavior prior to entering a study. If restraint or altered conditions are needed for the study, this should be planned ahead of time so that the animal will be comfortable with the new conditions prior to actual conduct of the study.

All animals should receive a physical examination prior to being used in a study. For acute studies this need be only cursory; for more involved procedures, more extensive examinations should be conducted. It is important to determine the presence of pre-existing abnormalities or conditions which would impact on the subsequent interpretation of study results.

Fluid and tissue collection

All personnel must be qualified to handle the species being used and to perform procedures necessary to collect the fluid or tissue. The method and volume of collection must be appropriate to the species, age and physical condition of the animal. Specific guidance on acceptable volumes and frequency of collection should be sought from the attending veterinarian. In instances where multiple samples are needed over a long period of time, surgical placement of indwelling catheters can facilitate sample collection.

Tissue collection via biopsy generally requires local, regional or general anesthesia, as well as appropriate aseptic techniques. The principles and procedures described in B-2-2 of this Guidebook should be adhered to under these circumstances.

Dosing and handling

Dosing with test chemicals is a routine use of laboratory animals which may result in distress due either to the nature of the chemical or the procedures involved in its administration, e.g., gavage. The IACUC may request that the veterinarian develop a chart of appropriate volumes which may be routinely administered by specified routes, and make this available to investigators preparing proposals.

Data collection

Some data collection can be accomplished by non-invasive techniques, such as arterial blood pressure monitoring by means of ultrasonic Doppler Flow Detection. Fetal development and EEG can be followed by the same techniques developed for humans.

In some instances chronic indwelling catheters or electrodes are used to monitor specific physiological parameters. The use of implantable telemetry can be preferable, as it reduces the risk of infection and damage from exposed wires.

Antibody production

Polyclonal antibody production

Of principal interest to the IACUC is the nature of the adjuvant, especially if it is Complete Freunds Adjuvant (CFA), injected with the antigen to augment the antibody response. CFA is commonly used, but it can cause severe inflammation, and can occasionally result in ulceration at the site of injection (CCAC, 1984). CFA should be used only for the initial immunization, with Incomplete Freunds Adjuvant (IFA) used for subsequent booster injections. Other adjuvants should also be considered, and CFA and IFA used only if no appropriate alternatives are available. Footpad injections are strongly discouraged and frequently prohibited by institutions.

Monoclonal antibodies

The production of monoclonal antibodies is a two step process. First, an animal (usually a mouse) is immunized to generate antibody producing cells which are fused with a tumor cell line. The second step is to perpetuate the antibody secreting cells either in culture, or by injection into the peritoneum of mice to yield ascites. The yield for *in vivo* production of antibody is as much as two thousand fold greater per unit volume compared to *in vitro* production.

To produce ascites in mice, the animals must be primed with pristane. The volume of oil used is an important consideration. Pristane causes irritation of the peritoneum, secretion of fluid into the peritoneal cavity and suppression of the immune response to the growing tumor. The mouse is injected with approximately three million hybridoma cells and the fluid accumulating in the peritoneum collected. The pris-

tane, the ascites tumor and the removal of the fluid are all potential sources of distress.

Chronic pathological states/disease induction

The justification for inducing chronic states must be carefully thought through and limits of allowable disease condition for the animal predetermined. A full schedule of monitoring, particularly for potentially painful conditions, must be included in any proposal presented to the IACUC. The study of naturally occurring pathological models is preferable to inducing such states artificially.

Antibody References

McGuill, M. W., and A. N. Rowan. 1989. Refinement of monoclonal antibody production and animal well-being. ILAR News 31(1):7-10.

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Osebold, J. W. 1982. Mechanisms of action by immunologic adjuvants. J. Am. Vet. Med. Assoc. 181:983-987.

Amyx, H. L. 1987. Control of animal pain and distress in antibody production and infectious disease studies. J. Am. Vet. Med. Assoc. 191(10):1287-1289.

B-2-5.
Role of the Attending Veterinarian

Introduction

Institutions using animals for teaching and research are required by law to have an attending veterinarian associated with their animal care and use program, unless they either use only rats and mice or receive no federal funds. Institutions with small programs often opt for a veterinarian as a part-time consultant. The veterinarian's overall responsibilities remain the same in all cases.

Qualifications

The veterinarian participating in a laboratory animal care and use program should have training or experience in attending to the species of animals maintained by the institution. Formal courses are now available for graduate veterinarians at a number of government, academic and commercial institutions which prepare the veterinarian for certification by the American College of Laboratory Animal Medicine (ACLAM). Alternatively, veterinarians may qualify for ACLAM certification by working in a laboratory animal resource program.

Responsibilities

The chief responsibility of the veterinarian is to provide for the health and welfare of the animals. The veterinarian must coordinate with the technical staff to ensure adequate daily animal husbandry. The details will depend on the species of animals employed and the nature of the activities in which they are used, but in all cases the care must comply with USDA Regulations and PHS Policy.

One of the prime mechanisms for ensuring high-quality laboratory animals is to purchase them from reputable vendors who produce pathogen-free stock. Generally, rodents and rabbits are purpose-bred. Certain states have passed legislation requiring that cats and dogs to be used in research be bred specifically for that purpose. Random source or wild-caught animals are not bred by the supplier but are obtained from a variety of sources, including pounds, shelters or farms which are not subject to the same standards. Before their use, clinical evaluation and conditioning of these animals is required to ensure that they are not carrying diseases which can be transmitted to other animals, including humans.

Although selection of high-quality laboratory animals has reduced the prevalence of infectious diseases in research institutions, additional preventive medical programs, conducted under the guidance of the attending veterinarian, continue to be important for maintenance of healthy animals. These programs include immunization against disease-causing agents; surveillance of colonies for specific infectious microbial agents; prophylaxis utilizing pharmaceutical agents; isolation and quarantine of incoming animals; and separate housing of animals according to species and source.

While such programs are successful in reducing the incidence of disease, illness and injury still occur in laboratory animal colonies. The veterinarian is responsible for monitoring animal health and providing adequate diagnosis and treatment of animals when illness or injury dictates veterinary medical care. The veterinarian may delegate responsibility for care to trained technical staff, but he/she must always be available to provide for rapid diagnosis and treatment.

Specific areas requiring the veterinarian's attention are the utilization of suitable anesthetic and analgesic agents; appropriate selection of species for research projects; ensuring that surgical procedures are performed properly and that pre- and post-surgical care are adequate. The veterinarian should discuss with investigators the design and implementation of their study proposals using animals and may provide writ-

ten guidelines dealing with these and other issues. Consultation between the investigator and the veterinarian before submission of a proposal to the IACUC may address many of the committee's concerns and expedite the review process.

USDA Regulations require institutions utilizing animals in research and teaching to provide training and instruction to personnel on humane methods of animal maintenance and experimentation. The veterinarian and the animal resource program staff, in conjunction with the IACUC, are usually responsible for providing such training.

At some institutions, the veterinarian or his/her staff may become directly involved in activities involving animals as a coinvestigator providing clinical or surgical expertise to the study. Veterinarians may also be principal investigators and be responsible for their own research programs. In such situations, the committee has the same obligation to review and approve the proposed activities.

The Policy requires institutional occupational health programs to include personnel who work in the animal resource facilities or whose activities include substantial animal contact. The veterinarian, in cooperation with appropriate health and safety officials at the institution, is responsible for the implementation and execution of the aspects of the program which are concerned with animal health and safety issues.

The Veterinarian and the IACUC

The veterinarian's role on the IACUC is mandated by USDA Regulations and the PHS Policy. Institutions employing several veterinarians may appoint more than one to the IACUC, but all institutions regardless of size must have at least one veterinarian as a member of the IACUC.

The veterinarian should keep abreast of current literature on comparative medicine and laboratory animal science. The knowledge gained often leads to suggestions for alternative techniques, models, or species which may augment the study design and help ensure completion of the proposed study.

B-2-6.
Personnel Qualifications

Investigator qualifications

If valid results are to be obtained, it is important that the investigators concerned have adequate knowledge and experience in the techniques used. USDA Regulations and PHS Policy put responsibility on the research institution to ensure that all personnel involved in animal care and use are appropriately qualified to conduct the proposed activities.

These federal requirements have led to the need for definitive outlines and documentation of instructional methods employed by institutions. The specific programs established are dependent upon a number of factors including outside requirements, institutional philosophy, and types of studies being performed.

Development of an educational program

Program design:
The institution is the legally responsible entity, but the practical development and implementation of an education program will be done by the IACUC, the veterinary staff and the investigators using animals. Program coordination is best achieved by either of the first two, but specialized procedures will rely on the latter. Outside consultants can also contribute to specific areas. The program must be flexible in design so that a heterogeneous group of investigators, technicians, students, IACUC members and veterinarians can be accommodated.

Program content:
[See Table 3]
The content of educational programs will be governed by legal requirements and by the specific scientific activities conducted at the institution. Certain basic procedures will be common to most programs, for example, blood sampling, injection methods, anesthesia and analgesic use. The investigators must also be familiar with the means to correct perceived deficiencies of animal care and treatment. They must be aware of information sources for optimal methods and methods to avoid unnecessary duplication of studies. Instructional methods should be designed to heighten the users' sensitivities to their animals and any potential adverse effects to these animals as a result of the procedures used. Review of proposals by the IACUC will highlight areas for inclusion in instructional programs.

Instructional methods:
These can include a variety of approaches ranging from individual instruction, the provision of self-instructional materials, institutional handbooks containing basic general information, and library support including audiovisual materials and organized courses. A newsletter is also an effective way of communicating to the variety of people involved in animal care and use.

Table 3
Required Contents for an Institutional Training Program

Training and instruction of personnel must include guidance in several areas.

(1) Humane methods of animal maintenance and experimentation, including:

[i] the basic needs of each species of animal;

[ii] proper handling and care for the various species of animals used by the facility;

[iii] proper pre- and post-procedural care of animals; and

[iv] aseptic surgical methods and procedures.

(2) The concept, availability, and use of research or testing methods which limit the use of animals or minimize animal distress.

(3) Proper use of anesthetics, analgesics, and tranquilizers for any species of animal used by the facility.

(4) Methods whereby deficiencies in animal care and treatment are reported, including deficiencies reported by any employee of the facility. No facility employee, Committee member, or laboratory personnel shall be discriminated against or be subject to any reprisal for reporting violations of regulations or standards under the [Animal Welfare] Act.

(5) Utilization of services (e.g., National Agricultural Library, National Library of Medicine) available to provide information:

[i] on appropriate methods of animal care and use;

[ii] on alternatives to the use of live animals in research;

[iii] unintended and unnecessary duplication of research involving animals; and

[iv] the intent and requirements of the Act.

Source: USDA Regulations, 9 CFR Part 2, Subpart C, Section 2.31. Federal Register, August 31, 1989.

Evaluation of the program:
To remain useful, the program must be revised and updated to fit the needs of the individuals involved, and the legal requirements of the institution. The IACUC should monitor the instruction available and assess the capabilities of investigators and staff. The opinions of the individuals completing different components of the educational program should be solicited.

Additional instructional resources:
Instruction can be assisted by programs developed for technicians at local community colleges. However, it is important to have one unit at the institution responsible for coordination and oversight of all aspects of the educational program. AALAS conducts formal training and certification programs which can form an important component of the institutional effort.

References

AALAS Training Manual Series and Instructional Guide for Technician Training. Cordova, Tennessee.

Bennett, B. T. 1990. Essentials for Animal Research: A Primer for Research Personnel. National Agricultural Library.

Education and Training in the Care and Use of Laboratory Animals. 1991. Institute of Laboratory Animal Resources. National Academic Press.

B-2-7. Hazardous Materials

Introduction

The IACUC must pay particular attention to proposals employing potentially hazardous materials, including radioactive substances, infectious microorganisms and hazardous chemicals. These all have the potential of causing harm to animals in the facility and the personnel caring for them.

Some hazardous materials are strictly controlled by federal, state and local regulations and often an institution has a specific committee to deal with all instances of their use. Radiation Safety Committees (RSCs) and Institutional Biosafety Committees (IBCs) have been mandated by the federal government to ensure that certain radioactive materials and recombinant DNA materials, respectively, are handled safely. The role of these committees is often extended to consider research involving human and animal pathogens. The IACUC should be generally familiar with the responsibilities of the various safety committees and organizations at their institution and the institution should ensure that the functions of the committees are coordinated.

In addition to the various safety committees, institutions should have professional staff or resources available with expertise in handling chemical, biological and radiological agents.

Radioactive materials

The U.S. Nuclear Regulatory Commission (USNRC) directly, or by its State designee, issues licenses permitting institutions to procure, use and dispose of specified radioactive materials. These licenses do not cover X-ray machines, high voltage accelerators, electron microscopes and radioactive materials from sources other than reactor by-products, although these are all sources of ionizing radiation. Radiation safety committees usually cover all radioactive sources. They also monitor all procurement, use and disposal of these materials; therefore, their approval should be coordinated with IACUC review of any proposal involving radioactivity. General information on potential health risks from exposure to ionizing radiation can be found in the USNRC Regulatory Guide.

Biohazardous materials

Infectious diseases may arise in many animal studies, due to natural infections as well as those specifically induced as parts of experiments. Consensus biosafety guidelines have been established for the use of animals in research involving infectious agents (Biosafety in Microbiological/and Biomedical Laboratories). These guidelines provide a concept for assessing risks and selecting appropriate safeguards. Four combinations of practices, safety equipment and facilities are described.

Recombinant DNA experiments involving animals also require approval from the IBC. The IACUC should read the report from the IBC review of facilities, procedures and practices, and expertise and training of personnel for any given proposal subsequently submitted to the IACUC.

Hazardous chemicals

In addition to animal care concerns, activities using hazardous chemicals must also deal with chemical storage and disbursement procedures, dosage preparation and challenge procedures, and waste management and disposal practices. It is also necessary to determine whether the chemicals will be present in feed, feces or urine. A rigorous review to assure appropriate safety practices, containment equipment and facility safeguards is essential for animal experiments involving chemical inhalation. A strategy for assessing risks and selecting safeguards for experiments involving chemical carcinogens has been developed by NIH.

Proposals submitted to the IACUC may not include sufficient documentation to assess the adequacy of precautions to control exposure of personnel to the hazardous agents involved in animal experiments. The identification by the IACUC of protocols involving hazardous chemicals, e.g., the use of known carcinogens to induce tumors in animal models, determinations of carcinogenicity, mutagenicity, or teratagenicity, or acute toxicity studies, may be essential for institutional compliance with safety and health standards. The Occupational Safety and Health Administration (OSHA) laboratory standard, "Occupational Exposure to Hazardous Chemicals in the Laboratory," is of particular importance. The IACUC should be familiar with the requirement in this standard for a chemical hygiene plan for controlling exposures to hazardous chemicals. Written protocols may be required describing appropriate safety precautions and specific "designated areas" where hazardous chemicals will be used or stored.

One health and safety issue common to most IACUCs concerns the use of the inhalation agent ether for anesthesia and euthanasia. Ether forms explosive peroxide when stored in metal containers and must be used with special precautions because of its volatility and flammability. Ether must be used with special ventilation and kept away from flames or electrical ignition sources. Carcasses of ether-killed animals should be stored in well-ventilated areas and not incinerated until the ether is volatilized. Other inhalation anesthetics, e.g., halothane, methoxyflurane, nitrous oxide, although not without some degree of toxicity in an occupational setting, are less hazardous when used with proper precautions and a waste gas scavagening system. Another hazardous chemical routinely encountered in the laboratory environment is formaldehyde. Specific OSHA guidelines are available for handling formaldehyde and other chemicals. Material Safety Data Sheets, which provide useful information on specific hazardous chemicals, must be maintained on site for each hazardous agent present.

Hazardous waste

Animal wastes contaminated with radioactive materials, infectious agents or hazardous chemicals must be carefully managed to avoid human exposure or damage to the environment. Special efforts should be made in experimental design to minimize the generation of wastes containing hazardous chemicals. Those containing radioactivity in addition to hazardous chemicals are particularly difficult to deal with. Wastes containing infectious agents should be decontaminated, preferably in a steam autoclave, before disposal. Incineration is the recommended treatment for contaminated feed and bedding.

Institutional policies should be reviewed, and assistance sought from the professional health and safety staff, who have responsibility for hazardous waste management at the institution, when animal care proposals involving hazardous materials are received.

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B-2-8. Field Studies

Review of proposals involving field studies poses special problems for the IACUC since the federal requirements and standards focus primarily on laboratory animal care and use. Professional field biologists in organizations devoted to the study of fish, amphibians, reptiles, birds, and mammals have recently prepared guidelines for field work with these animals, and they form a useful reference. The report of a recent workshop sponsored by the National Science Foundation is also of value.

Unique concerns in the field include the impact of a given proposal on the native populations of animals at the experimental site. This can be due to the use of enclosures, or, more indirectly, the effect of changed behavior of the study animals on other populations in the vicinity.

The proposed study can be assessed by the IACUC according to a number of priority questions which are similar to those used for a laboratory-based proposal:

Species selection:
The most common and least sensitive species should be studied in preference to rare or endangered ones, or ones known to be particularly timid and susceptible to distress. Consideration should be given to whether the

population is stable, growing, declining or marginal. If either of the latter is evident, careful attention must be given to the potential impact of the proposal.

Site selection:
Many animals live in a variety of habitats and the choice of a study site conducive to obtaining maximal results with minimal disruption should be given priority. Also, the impact of other human enterprises on the site should be considered, for example, agriculture, tourists, hunting, and fishing may all disrupt a study. The ownership of the site, and whether permits are required to gain access or to conduct experiments, are also crucial considerations. The investigator must be able to assure the IACUC that all the necessary permits have been obtained.

Methodologies to be employed:
If animals are to be captured, methods and numbers should be detailed in the proposal. Measures taken to alleviate distress and injuries should be described. Some discussion of the potential impact of capture on the subsequent behavior of the animals should also be included. If the animals are to be monitored individually, the investigators must indicate whether they plan to follow the animals by their natural markings or whether they will be artificially marked. If the latter, a clarification of methodology and potential trauma is necessary; e.g., paint markings may increase visibility to predators. Often the fact that a method has been used traditionally is presented as a justification; for non-endangered populations and if minimal distress is involved this is usually adequate.

Site manipulations may include the removal of prey, predators, or the addition of either. The latter is rarely justified if non-native species are involved. It may be proposed to erect fences to limit the movement of populations. Individual animals may be treated to alter their behavior by surgery or drugs, or their markings changed to assess responses by the community. Individual animals may be periodically removed to take tissue samples. When these individuals are meant to survive, aseptic practices should always be employed for such surgical procedures. In all of these instances any potential pain or distress to an individual animal must be assessed and the investigator's justification evaluated in the context of the value of the data to be obtained. Consideration should also be given to additional data that might be obtained at no further cost. Potential long term effects on individual animals, their community, and other species in the vicinity must also be evaluated.

Clearly many of these questions are difficult to answer definitively, but their consideration will help the IACUC judge the potential impact, as well as the potential value, of the study proposed. Such questions can be expected to assist the investigator in obtaining maximum information from his study with minimum negative environmental impact.

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B-2-9.
Death as an Endpoint
(See Table 4)

Background

Since it provides an objective and unequivocal data point, death has been used as an endpoint in cancer, infectious disease and other animal studies, especially for regulatory purposes (e.g., drug safety/efficacy studies). Increased public interest and regulation have led to a reevaluation of its appropriateness. Much of the current concern arises from the use of LD50 tests for chemicals and drugs to determine acute toxicity measures. In the main, euthanasia provides tissues more appropriate for subsequent study and alleviates potential suffering by the animal. Hence, euthanasia is often feasible scientifically, as well as ethically.

The *routine* use of death as an endpoint should be discouraged. Endpoints other than death must always be considered and should be used whenever the research objective makes it possible. Use of death as an endpoint must be justified in writing in the proposal and its use must be approved by the IACUC prior to

beginning a study. Drugs or techniques to alleviate pain or distress preceding death must be used unless they would interfere with the scientific objectives of the study. A proposal foregoing the use of anesthetics, analgesics or tranquilizing drugs must be extensively justified to the IACUC.

Alternative endpoints to death for studies with potentially lethal outcomes

In many types of studies where lethality was previously considered essential, alternative endpoints are now proving to be more scientifically sound and ethically acceptable. Factors to consider include percentage loss of body weight, respiratory changes, cardiovascular alterations, neural indicators, inflammation, etc.

Where survival data are required, euthanizing animals when they become moribund has proven useful. This requires the investigators to define a moribund state prior to initiating the study. They must also ensure that throughout the study the personnel monitoring the animals have appropriate qualifications and choose sufficiently frequent observation points. The latter will be determined by the species, the onset, severity and duration of expected clinical signs, and other specific characteristics of the agent being tested.

Examples of studies involving potential lethality

Anti-neoplastic drugs frequently have toxic side effects. This poses a particular problem, as the drugs are normally administered close to their toxic dose in order to demonstrate their effectiveness. Whether imminent death is due to the cancer or the drug can be difficult to determine and can make euthanasia inappropriate.

Lethal, whole body irradiation, used to render the immune system incapable of rejecting grafts, seriously reduces an animal's ability to deal with infection, and causes dose-dependent radiation injury. Defined predeath endpoints can be impossible when only subtle differences exist between control and experimental groups.

Similar considerations should be given to acute toxicity tests for drugs and chemicals and to studies of infectious diseases which may cause a variety of lethal outcomes. They do not invariably require death, and sampling prior to death may actually reveal more information. In all cases alternative endpoints should be considered, as well as a careful evaluation of the minimum number of animals necessary for the study.

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Table 4
Example Alternative Endpoints for Studies with Potential Lethality

Alternative Endpoint	Example	Application
Tumor Characteristics	10% of normal body weight, necrosis, infection	Subcutaneous or intraperitoneal tumors and hybridomas
Peripheral Blood Cell Counts	Depends on cell type	Leukemias, infectious disease, anemia
Prolonged Inappetence/Cachexia	Loss of weight (20% of normal body weight) and/or condition	Metastatic disease, chronic infectious disease
Inability to Obtain Feed and Water	Paralysis, oro-facial or cervical lesions, other non-ambulatory condition	Many
Signs of Severe Organ or System Involvement	Respiratory: rapid or labored breathing, coughing, rales Cardiovascular: shock, hemorrhage, anaphylaxis Gastrointestinal: severe diarrhea or vomiting Peripheral Nervous System: flaccid or spastic paralysis CNS Signs: circling, blindness, dementia, convulsion Integument: extensive hair loss, inflammation	Toxicity testing
Moribund or Pre-moribund State	Define with specific clinical signs and euthanize when reached	Many

C.
IACUC Oversight of Animal Care and Use Program

C-1.
Policies, Procedures and Responsibilities

C-1-1.
Facility and Program Review

Introduction

Under PHS Policy and USDA Regulations, the IACUC must inspect all institutional animal facilities every six months. These inspections provide an ongoing mechanism for ensuring that the institution maintains compliance with the applicable animal care and use policies, guidelines and laws. They can also benefit programs for animal care by serving an educational function for the animal care personnel, research staff and IACUC members. Also, by giving the facility personnel a prior warning, the IACUC can assist an institution to prepare for subsequent visits by outside inspectors. The interaction of an IACUC and the animal care personnel at their institution should be constructive, and not adverserial, as both ultimately share the same goals of good animal care.

Staffing and scheduling inspection

The IACUC must schedule the inspections of facilities. This may be accomplished by assigning specific facilities to subcommittees which must contain at least two members as required by the USDA Regulations. No IACUC member should be excluded should he/she wish to attend a particular inspection, and additional ad hoc consultants may be used. The inspection team must have a working knowledge of the *Guide* and USDA Regulations in order to fully evaluate the facilities which are being inspected. Section C-2 of this Guidebook also provides general guidance in this regard. It is helpful for the team to have a pre-prepared list of the categories to be inspected, such as sanitation, food and water provisions, animal identification, waste disposal, animal health records, environmental control, staff training, etc.

The IACUC may determine whether the supervisory personnel of various facilities should be notified of the date and time of an inspection. Advance notification allows individuals to be available to answer questions, but an unexpected visit shows the facility during usual operations.

Performing inspections

An updated list of all facilities to be inspected should be maintained by the IACUC. All proposals submitted to the IACUC must contain details of all locations at which animal research is to be performed. The USDA Regulations require inspection of the centrally designated or managed animal resource facilities as well as any other animal containment facilities in which animals are kept for more than twelve hours. PHS Policy requires inspection of all surgical facilities and areas in which animals are maintained longer than 24 hours. It is helpful to keep a list of all facilities by room number, use, species and deficiencies noted in the last inspection. For satellite areas a contact person is useful. For facilities with multiple rooms, a map will assist the inspectors.

Notes should be taken throughout the visit to assist in preparation of the final report. Apparent deficiencies should be discussed with the person in charge of the facility to ensure that the team's perception of the situation is correct. In some cases an apparent deviation will be due to the experimental proposal in process, for example, withholding of food prior to surgery.

Documentation

After the visit a formal report is prepared. Any deficiencies must be categorized as minor or significant. The latter is defined, by USDA Regulations and PHS Policy, as one of significant threat to animal health or safety. A plan and timetable for correction of all deficiencies must be included in the final report. All individuals to be involved in the corrections should be consulted to ensure that the plan is realistic. If the institution is unable to meet the plan, the IACUC through the Institutional Official must inform Animal and Plant Health Inspection Service (APHIS) officials within fifteen working days of the lapsed deadline. If the activity is federally funded, the relevant agency also must be informed.

The report must be reviewed and approved by a quorum of the IACUC, and in cases involving USDA Regulations, be signed by all those who accept the report. Minority views should be included in the final document. A copy is then sent to the Institutional Official and must be kept on file for a minimum of

three years. It is often useful for the report to be delivered in person in order to emphasize the findings and plans for action. Annually, the institution must notify OPRR of the dates of the semiannual inspections and the dates the report was submitted to the Institutional Official.

C-1-2. Program Evaluation

Both the PHS Policy and USDA Regulations include a requirement that semiannually the IACUC conduct an evaluation of the animal care and use program. Neither of these documents includes specific guidance regarding the mechanisms or procedures to employ in conducting this evaluation. OPRR has recommended that institutions use the Table of Contents of the *Guide,* exclusive of the facility and physical plant chapters, as an outline for program evaluation. The USDA Regulations refer institutions to other portions of those Regulations as a basis on which to conduct this program evaluation.

Key aspects of an animal care and use program that should be emphasized in the semiannual evaluation include IACUC functions and procedures, including proposal review practices, provisions for dealing with "whistle blower" or other concerns regarding animal care and use, and the procedures employed to meet reporting requirements. In addition, the institution's occupational health program, veterinary care procedures and personnel qualification review process should be evaluated. Specific procedures to accomplish program evaluation may include presentations by appropriate individuals, e.g., the institutional veterinarian, occupational health personnel, etc. Written institutional policies such as standard operating procedures may be reviewed and modified if necessary.

Program evaluation deals principally with administrative aspects of the animal care and use program. In most instances these aspects will not change nor need to be modified with the same aspects of the facility or physical plant. Thus, when large changes are made in program aspects, a comprehensive evaluation by the committee should be conducted, while the review of that aspect six months later may be merely a brief evaluation of its implementation to date. Ongoing review of established practices allows the opportunity for institutions to detect a gradual change in practices from written procedures, thereby allowing modification of one or the other as appropriate. Institutions that are AAALAC accredited will find their pre-site visit package helpful in identifying areas for inclusion in the semiannual evaluation.

C-2. Animal Health and Husbandry

C-2-1. General

The *Guide* states "Proper management of animal facilities is essential to the welfare of animals, validity of research data, and health and safety of the animal care staff. A good husbandry program provides a system of housing and care that permits animals to grow, mature, reproduce, and maintain good health. Good husbandry minimizes variations that can modify an animal's response to experimentation. Specific operating practices depend on many subjective and objective factors unique to individual institutions. Well-trained and motivated personnel can often ensure high quality animal care, even in institutions with less than optimal physical plants or equipment."

Adequate animal husbandry practices and health maintenance are facilitated by well-constructed and maintained caging or housing systems. Animal housing must not only confine the animal(s), but also should promote animal comfort and safety by providing sufficient space and other accommodations for normal postural and behavioral activities. The USDA Regulations and the *Guide* provide minimum cage size requirements/recommendations for most common laboratory animal species.

Cages should allow for adequate ventilation and enable ready access to food and water receptacles. They should be constructed of materials that can be easily cleaned and sanitized, with common materials including polycarbonate plastic, stainless steel and fiberglass. Unsealed wood generally is not acceptable in animal cages or pens, as it can not be satisfactorily cleaned or sanitized.

Many animal species are social in their natural state. Some, such as the dog and cat, are readily socialized to humans. Encouragement of intra- and interspecies socialization is recommended by USDA Regulations and the *Guide* and is widely recognized as advantageous to animal well-being and the research endeavor. A sound husbandry program will include provision of the opportunity for animals to establish and/or reinforce social activities, including physical exercise.

Environmental factors can have a profound effect on the health and well-being of animals as well as the outcome of experimental manipulation. Temperature, humidity, air pressure and rate of turnover and noise levels all may affect animal well-being and research results. A review of an animal care and use program should include consideration of environmental standards adopted for the facilities with adequate justification available for significant deviations. While environmental control in outdoor facilities is much less stringent, acceptable ranges in temperature for several species are available in USDA Regulations. Reliable methods for monitoring environmental control systems should be in place. Redundancy in heating, ventilation, air conditioning, and lighting systems is highly desirable. Protocols for caring for animals and personnel during failures in environmental control systems should be established with personnel informed of proper procedures.

It is imperative that research animals be adequately and appropriately identified and that records pertaining to individual or groups of animals be maintained. A wide range of acceptable identification methods can be employed, ranging from cage cards to individual animal tatoos. The formerly widespread use of toe-clipping to identify individual rodents is now generally discouraged, with tail tattooing or ear-tagging in more common use. Animal records may consist of only a cage card or may involve detailed individual animal information, depending principally on research requirements. Of paramount importance for research facility animal records is prominent display of the investigator's name, location and the IACUC-approved protocol number.

C-2-2. Animal Care

a. Feeding

All animals should receive food that is palatable, free from contamination and of sufficient quantity and nutritive value to maintain their good health. Specific diets should be selected based on the needs of each species, with special consideration of the requirements for vitamin C by guinea pigs and some species of nonhuman primates. Animals should be fed at least once a day except under conditions of hibernation, veterinary treatment, pre-procedural fasts, or other justified circumstances.

It is known that standard commercial dry bulk foods, when stored properly, retain their nutritional value for six months (three months for those containing Vitamin C). To assure that age deterioration of food does not occur, the milling date should be known (it is usually stamped on each bag), and bags should be stored so that the oldest is used first. Large amounts of food should not be stored in animal rooms. Small quantities may be kept in animal rooms if stored in tightly covered, leak- and vermin-proof containers; these should not be moved from room to room.

Food should be provided in receptacles that are accessible to all animals in a cage or pen and placed so as to minimize contamination. Food receptacles should be easily cleaned and sanitized, and those functions performed on a schedule that meets *Guide* and USDA Regulation requirements. With limited exceptions, e.g., germ-free animals in microisolator cages, food should not be placed on the bottom of the cage. Although some species may prefer this presentation, it results in waste and contamination of the food.

b. Watering

Potable drinking water should be available continuously or provided as often as necessary for the health and well-being of the animal, considering the animal's species, age, condition and any research requirements. Water may be provided in receptacles, e.g., bowls, bottles or via automatic watering systems. Whatever method is used, care should be taken to ensure that water does not become contaminated and is actually available. Sipper tubes and automatic watering devices should be checked routinely for patency. Water bottles generally should be replaced rather than refilled.

c. Bedding

Bedding may be used in the housing of a variety of commonly used laboratory animals. Bedding material should be absorbent and free of any substances that might harm the animals or alter research data. Cedar and pine products can affect liver enzymes which may in turn affect immunologic or other physiologic parameters.

Animals may be placed directly on bedding material, a common practice with many rodent species, or it may be placed under a wire or slat-bottom cage. This latter method is used occasionally for rabbits, dogs, nonhuman primates and farm animal species. Bedding should be changed as often as necessary to

keep the animals clean and dry and the animal room relatively odor free.

d. Animal Activity

There is widespread disagreement among experts and the general public regarding laboratory animals' needs for supplementary physical and mental stimulation. Current USDA Regulations reflect the will of Congress in the 1985 Amendments to the Animal Welfare Act in that they require institutions to develop plans for: (1) providing dogs the opportunity to exercise; and (2) enhancing the environment of nonhuman primates so as to promote their psychological well-being. Conditions and requirements for these plans are included in the Regulations. Where no regulatory requirements exist, the decision to supplement activity in animals should be made by the institution, in most cases through the IACUC and based on recommendations of the veterinarian, in consultation with the investigator. Factors to be considered in this decision include the animal's species-specific characteristics, temperament, physical condition, previous housing conditions, nature of the research and anticipated duration of housing. There is widespread agreement that the best enhancement of environment for an animal that is social in nature is another animal. Group housing of most species generally is encouraged, recognizing that research requirements may preclude it and some negative effects (e.g., fighting, potential for disease transmission) may be seen.

e. Emergency, Week-end and Holiday Care

Laboratory animals must be observed by qualified personnel every day in order to ensure their health and well-being, as well as to promote sound research practices. Skilled assistance, including veterinary care, must be readily available at all times. Names and telephone or pager numbers of those assigned these responsibilities should be prominently displayed in the facility.

C-2-3. Facility Maintenance

a. Cleaning and Sanitation

Cleanliness and sanitation are essential to the operation of an animal facility. The *Guide* and USDA Regulations set forth recommended frequencies and methods for cleaning and sanitation of facilities, equipment and accessories. In general, the frequency and methods should ensure that animals are maintained in a clean, dry environment, free from exposure to harmful contamination and excessive animal odors. Cleaning equipment such as mops and pails should not be moved from room to room.

The most efficient and effective method of cleaning and sanitizing cages and accessories (e.g., feeders, water bottles, sipper tubes) is the use of a mechanical washing machine that provides rinse water temperature of at least 83 C (180 F). Alternatively, portable high pressure spray washing and disinfection may be used. Least efficient and effective is hand washing and disinfection of such equipment. The supply lines of automatic watering systems should be flushed and disinfected on a regular basis.

b. Waste Disposal

A research animal facility generates a significant amount of waste that must be removed and disposed of on a regular, frequent basis. Disposal methods, including incineration and removal to land-fill must conform to federal, state and local requirements. Some jurisdictions consider all soiled animal bedding from a research facility to be "medical waste," with consequently more stringent disposal requirements.

If waste must be stored while awaiting disposal, the storage area should be outside the animal holding and clean equipment areas. Animal carcasses and tissues require a separate cold storage area and regularly scheduled removal. Hazardous waste, including carcasses of animals exposed to radioactive or biohazardous agents, must be adequately sterilized and/or contained prior to removal and disposal.

c. Vermin Control

The research animal facility is an active place, with frequent movement of personnel, animals, equipment, containers, food and bedding. This creates ideal conditions for the introduction of vermin from arthropods to wild rodents. Vermin control programs are complicated by the potential for harm to animals and personnel, as well as interference with research data by many commonly used pesticides. The most effective program combines elimination of all entry and harborage sites, with good waste disposal and personnel training.

C-3. Occupational Health (See Table 5)

Purpose of occupational health programs

The health of individuals working in animal care programs is an area of institutional concern. PHS Policy and the *Guide* identify the need for an occupational health program for all personnel who work in laboratory animal facilities or who have substantial animal contact. The emphasis of such a program is the prevention of illness, but it also includes provisions for early diagnosis and treatment when such illnesses occur.

Elements of an occupational health program

An effective program will have the following components: 1) pre-placement medical evaluation; 2) periodic medical surveillance; 3) educational component; 4) provisions for treating illness or injury; and 5) provisions for consultation with other professional staff. The specific elements will be dictated by the extent and nature of the employee's exposure [see table].

Pre-placement and periodic medical evaluations:
Pre-placement evaluations are conducted to ensure that the individual is capable of the demands and exposure of the job, and also to provide a medical reference baseline. The evaluation may include: clinical history, physical examination, spirometry, baseline tests such as TB test and serum sample collection, appropriate immunizations, educational/instructional component and appropriate feedback to the employee on all test results. Specific tests will depend on the species of animals and the nature of the procedures employed.

Periodic evaluations allow detection of early stages of disease, updating of immunizations and a re-evaluation of medical restrictions.

A uniformity in the evaluation of different individuals and the same person at different times is important to enable accurate comparisons to be made. These comparisons may allow a possible problem to be identified and corrected before it becomes a major health hazard.

Education:
There are ethical and legal requirements to inform individuals of health risks and precautions which affect them. This must be part of an employee's overall orientation and job training. Some institutions rely on formal courses.

Medical care and treatment:
In addition to established mechanisms for reporting and treating accidents and injuries, the institution should have access to medical expertise in zoonotic diseases and other health risks associated with laboratory animal care. Such expertise will greatly assist in the recognition of diseases, allergies or musculoskeletal overuse syndromes associated with animal care. Good communication with medical staff will also facilitate better management of the health of animal care personnel and minimize repeat injuries and infections.

Specific medical concerns for individuals working with laboratory animals

Allergy and musculoskeletal injury constitute the primary health risks to individuals using and caring for laboratory animals. Allergies are a significant problem, and can be reduced by the provision of protective equipment to affected personnel. Musculoskeletal injuries can be minimized by good laboratory planning, use of transport equipment such as carts, and training in lifting and equipment use.

Infectious diseases also form a significant risk depending on the species and health status of animals involved and the level of exposure to them by animal care personnel. Infectious diseases to which animal care personnel may be exposed include a number of viral infections, some of which can be extremely serious, for example rabies. In addition, infections acquired from live animals, animal tissues and excreta can serve as a source of zoonoses. Careful monitoring and quarantine of any animals with potential viral or bacterial infections is a crucial part of any animal care program. Particular care must be taken in all facilities handling primates as they are likely to carry infections which can be transferred to humans, for example, Herpes Virus Simiae (Herpes B) and tuberculosis. Routine TB testing is essential.

Animal bites and scratches are hazards common to animal facility personnel. All cases should be documented. Tetanus prophylaxis should always be considered and, depending on the species, rabies prophylaxis and antibiotics arranged.

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Table 5
Occupational Health Program for Animal Handlers

Species Used/ Other Factors	Extent of Animal Contact: Direct Regular Contact (8hrs/week or more)	Direct Contact Limited Exposure (less than 8hrs/ week or more)	No Direct Contact, Occasional Exposure
Small Animals (Rabbits, Rodents Birds)	1 2 5	1 2 5	
Dogs, Cats and Feral Animals	1 2 4	1 2 4	
Primates	1 2 3 8	1 2 3 8	3
Farm Animals	1 2 6	1 2 6	
Amphibians, Reptiles, Fish and Other Cold-Blooded Animals	2	2	
Infectious Disease Studies (Class III or Higher)	1 2 7 8 9	1 2 7 8 9	1 2 7 8 9
Work with Animal Tissues	7	7	7

Code Number	Procedure
1	Pre-Employment Physical Exam (including serum for banking)
2	Tetanus Immunization (every ten years or following known injury on advice of physician)
3	TB test (every six months)
4	Rabies Immunization
5	Pre-Employment Allergy Evaluation and Education
6	Special Education on Large Animal Diseases
7	Special Consideration by Infectious Disease Committee
8	Post-Employment Physical (including serum for banking)
9	Annual Physical Exam

D.
IACUC Evaluation of Animal Welfare Concerns

D-1.
Policies, Procedures and Reporting (See Table 6)

Introduction

One of the basic functions of the IACUC, as specified in the USDA Regulations is to "review and, if warranted, investigate concerns involving the care and use of animals at the facility resulting from public complaints received and from reports of noncompliance received from laboratory or research facility personnel or employees" 9 CFR Part 2, Subpart C, Section 2.31 (c)(4). Also required under 9 CFR Part 2, Subpart C, is training of personnel in the "methods whereby deficiencies in animal care and treatment are reported, including deficiencies in animal care and treatment reported by any employee of the facility." The institution should have established procedures for reporting, receiving and handling allegations of animal mistreatment or other noncompliance.

Definition of mistreatment and non-compliance

Mistreatment is physical or psychological, wrongful or abusive treatment of an animal. This is a broad definition and clearly, gray areas exist which the IACUC must interpret carefully. Fortunately, it is rare that mistreatment is intentional. Noncompliance means that procedures or policies are not being followed, and this may stem from confusion or misunderstanding. There are areas of overlap between mistreatment and noncompliance, and the procedures for handling both are very similar.

Institutional policies

The highest administrative levels must advocate the finest animal care and by so doing assure the public, researchers, employees or students that there is a true desire to investigate allegations of mistreatment or noncompliance. The IACUC and veterinarians must perpetuate the same attitude. There must be no implication that reporting such instances could be detrimental to an individual's standing within the organization. Indeed, the USDA Regulations provide specific protections under the law. [9 CFR, Part 2, Subpart C 2.32 (c)(4)]

It is prudent to have established procedures for handling allegations of mistreatment or noncompliance before any such allegations are raised. Addressing complaints against the appropriate use and care of animals is very difficult and only with a clear set of guidelines can this be performed in a thoughtful and systematic manner. A direct statement to the IACUC, or its designated subcommittee, helps empower the IACUC to deal with such allegations.

Reporting allegations:
It is not always obvious at what level of alleged mistreatment or noncompliance the IACUC should become involved. Frequently the attending veterinarian, animal care personnel and investigators can work together to prevent or correct problems. However, serious or repeated problems always demand the involvement of the IACUC. If in doubt, it is better to report, as this may well protect the institution, the complainant, the alleged violator(s) and, of course, the animals.

A variety of ways can be provided in which to report allegations. These may include conversations with, or letters to, members of the IACUC, the veterinary staff or the Institutional Official. As dictated by the USDA Regulations, there must be no restrictions on who can report an alleged incident and no threat of reprisals against those reporting perceived mistreatment or noncompliance. Whatever the route, the information should be quickly relayed to the chairman of the IACUC.

IACUC responses to complaints:
Ideally, all complaints brought to the IACUC's attention will be fully documented and signed. This does not always occur, and judgment must be used to evaluate the significance of undocumented complaints. Whatever the case, the allegation must have sufficient substance for the chairman to proceed further. An allegation has no substance until proven, and should remain confidential to the extent possible to protect all concerned. If a complainant has openly identified him/herself, it is appropriate that receipt of the allegation be acknowledged. The IACUC must decide the level to which they wish to keep the complainant informed during the investigation.

IACUC procedures for the investigation of a complaint:
The institutional policy for handling allegations should clearly specify who will be responsible for dealing with the complaint. For example, the IACUC as a whole, or

a subcommittee, could be identified. In all cases, the results of an investigation must be considered IACUC actions and all members must have the opportunity to present minority views. All persons involved should be informed of the purpose of the investigation and the manner in which it will be conducted. Those against whom the complaint is addressed should have an opportunity to explain their side of the issue. As much documentation as is reasonably needed should be collected. Interviews and inspections of facilities may be needed. In some cases it may be necessary to review animal receiving records, housing and health records, billings, memos and other written materials. When allegations result in IACUC investigations, the results should be made available to all parties involved, including the Institutional Official who is ultimately responsible for taking corrective action.

Institutional responses:
This is influenced by legal requirements, institutional policy and the nature of the investigative findings. If the violation is verified by the IACUC, then the IACUC is empowered under USDA Regulations and PHS Policy to suspend a previously approved project. If the activity is supported by PHS funds, the IACUC through the Institutional Official must file a full report to OPRR. In cases where there is sufficient evidence of serious noncompliance, it may be prudent for the IACUC to suspend an activity pending the outcome of a full investigation. In these cases, a preliminary report should be sent to OPRR, through the Institutional Official, with a promise of a full report upon completion.

The Institutional Official in consultation with the IACUC, has the power to impose further sanctions on an investigator found responsible for mistreatment or noncompliance. The institution must also consider whether to publicly announce its findings. While each case must be considered individually, all cases will result in precedents being set, and the implications of these must be considered.

Table 6
Procedures Used for Consideration of Allegations of Noncompliance

Institution policies that encourage and support high levels of animal care and welfare.

Establish guidelines for the investigation of complaints, including reporting lines, authority to impose sanctions, assurances of due process, appeal procedures and confidentiality.

Provide multiple channels for personnel to bring complaints or comments to the IACUC. Personnel should receive instructions on methods of raising concerns and on whistle-blower protections against reprisals as required by law.

The IACUC determines if a complaint has sufficient substance to be investigated further.

Investigative Committee of the IACUC informs alleged violator of nature of complaint and investigative procedures that will be followed.

Investigative Committee examines pertinent documents, animals, procedures, personnel, etc.

Investigative Committee presents findings to IACUC for endorsement with appropriate recommendations to Institutional Official.

Institutional response dictated by nature of findings, legal requirements and institutional policies.

E.
IACUC Recordkeeping and Reporting

E-1.
Policy and Procedures

Introduction

Both PHS Policy and USDA Regulations include reporting and recordkeeping requirements. Tables 7A-7E compare the two. It is crucial that the responsibility for preparing reports be clearly delineated within a given institution. The persons assigned the task must be knowledgeable of federal requirements and the institution's animal care and use program. He/she must also be aware of the Freedom of Information Act (FOIA) and any state open records laws. Many of the reports written may be accessible under such laws, and particular care must be taken to avoid using language that may be misconstrued by the lay public. Ideally, the recordkeeping responsibilities will be assigned to one office. The IACUC's role varies depending on the administrative structure of the institution. In some instances animal resources personnel or grants and contract offices may contribute, or the responsibility may lie solely with the IACUC and its support staff.

PHS Animal Welfare Assurance

Institutions receiving support from the PHS for activities involving animals must provide an Assurance of Compliance (Assurance) with the PHS Policy. The Assurance is a written agreement in which the institution outlines in detail its policies and procedures for such treatment (Table 7A for details).

The Assurance must be signed by the Institutional Official, an individual who has the authority to make the commitment on behalf of the institution, guaranteeing that PHS Policy will be complied with. The Assurance is submitted to OPRR which reviews, negotiates any necessary details and approves the Assurance. OPRR issues an Assurance number to the institution and maintains the Assurance on file in its office.

USDA Facility Registration:

USDA Regulations require that each research facility register with the Secretary of Agriculture using a standardized form. Registration is required if a facility has USDA-regulated species on its premises. The form is submitted to APHIS, and the Regulatory Enforcement and Animal Care (REAC) Sector Supervisor for the state in which the facility has its principal place of business (see Table 7A for summary).

At academic institutions, the submission is usually made by the institution, not the individual departments or schools. Usually the Institutional Official also signs the USDA submission. The registration is updated every three years by completing a new set of forms provided by APHIS, REAC Sector Supervisor. The institution is required to notify the Sector Supervisor within ten days of any change in the name, address, ownership or operations affecting its status as a research facility. A facility which has not handled animals for two years may be placed in inactive status by Sector Supervisor. The registration can be cancelled by written request if a facility no longer uses, or intends to use, animals.

Annual Report

PHS:

At an institution with an approved Assurance, the IACUC must submit an annual report to OPRR through the designated Institutional Official (see Table 7B for details). This annual report, as well as all other information requested by or submitted unsolicited to OPRR, is accessible under FOIA. To minimize security risks, OPRR does not require, and institutions do not routinely submit copies of the semiannual reports required as described below.

USDA:

On or before December 1, each facility registered with USDA must submit an annual report to the APHIS, REAC Sector Supervisor, for the state in which the facility is registered. The report is a standard form and is usually prepared by the IACUC. It is signed by the CEO or Institutional Official and covers the previous fiscal year. Specific items to be included in the report are listed in Table 7B.

Semiannual Report of Facility Inspections and Program Evaluations

PHS:

PHS Policy requires that the IACUC inspect all facilities every six months, and prepare a report which is submitted to the designated Institutional Official. The report must contain a description of the nature and extent of the institution's compliance with the PHS

Policy and *Guide*; any departures must be identified and modifications proposed, with a plan and timetable for correction. Minor and significant deficiencies must be distinguished. The report must also identify any facilities which are AAALAC accredited, or accredited by any other professional body recognized by PHS.

USDA:
These requirements are essentially the same as those for PHS with three exceptions. First, the USDA Regulations include additional reporting requirements if the schedule and plan for correcting a deficiency is not followed. Failure to correct a significant deficiency in accordance with the specified schedule and plan must be reported in writing within fifteen business days by the IACUC, through the Institutional Official, to APHIS and any federal agency funding the activity. Secondly, USDA requires that reports be reviewed and signed by a majority of IACUC members. Finally, USDA does not require the identification of facilities accredited by AAALAC. Table 7C summarizes the differences between PHS and USDA semiannual reporting requirements.

Suspension/noncompliance explanation

PHS:
At an institution with an approved PHS Assurance, the IACUC must explain, through the Institutional Official, the circumstances and actions taken in the following instances:

1. any serious or continuing non-compliance with PHS Policy;
2. any serious deviation from the provisions of the NIH *Guide*; and
3. any suspension of any activity by the IACUC.

USDA:
If the IACUC suspends any activities involving animals, the Institutional Official files a report, in consultation with the IACUC. After reviewing the reasons for the suspension and taking appropriate corrective action, the Institutional Official is responsible for submitting a full explanation to APHIS and any federal agency funding the activity (see Table 7D).

Recordkeeping requirements

PHS:
These include IACUC minutes, individual proposal records, and basic reports and documents. These records must be accessible for inspection and copying by authorized OPRR or other PHS representatives.

The minutes must include records of attendance, activities of the committee, and IACUC deliberations. These minutes must be kept for three years. Individual proposal records include the application, proposed modifications and outcome of the review. These records must be maintained for the duration of the activity, plus an additional three years after completion. Basic reports and documentation include the Assurance document; semiannual IACUC reports, including minority views; and accrediting body determinations.

USDA:
These regulations are essentially the same as the PHS Policy for IACUC minutes and individual proposal records. Some differences apply to recordkeeping specifications. USDA does not require copies of Assurance documents or reports of accrediting bodies, but they do require that institutions maintain records from on-site, unannounced facility inspections conducted by APHIS officials. USDA also has specific regulations applying to each live dog or cat purchased, acquired, held, transported, euthanized, sold or disposed of. Responsibility for maintenance of such records generally lies with the animal resources office. USDA requires that the records be available to authorized APHIS or federal funding agency representatives, but material is not normally removed unless a violation has been alleged or an investigation is being undertaken.

Table 7E compares the requirements for the two agencies.

E-2. IACUC Staffing

The nature of the institution and the volume of animal-based research greatly influence the support staff requirements of an IACUC. Larger institutions with a high volume of proposals involving animals may require full-time administrative support staff.

IACUC staff generally are assigned responsibilities for: 1) screening proposals for accuracy and completeness; 2) distributing copies to Committee members; 3) keeping records of proposals received and Committee decisions on them; 4) coordinating and scheduling the Committee's meetings, facilities inspections and laboratory site visits; 5) correspondence; and 6) an information resource for investigators and Committee members, or regulatory issues and the status of proposals. It is essential that all proposals are assigned, copied and distributed, and that they are tracked appropriately.

The IACUC should have available grant applications submitted for PHS funding in order to ensure consis-

Table 7A
Federal Reporting Requirements

	USDA Research Facility Registration	PHS Institutional Assurance
Submit If	Animals covered by USDA Regulations on premises	Receiving PHS Support*
Submit To	APHIS, REAC Sector Supervisor (on agency forms)	Office for Protection from Research Risks
File By	Institution/Facility	Institution
Update	Every 3 years	Assurance approved for up to 5 years
Authorization	Signed by person with legal authority to bind organization	On letterhead and signed by Institutional Official
Other	**After submission of standard form:** APHIS supplies regulations and standards after submission Sign 2nd form acknowledging receipt and agreeing to comply Submit to APHIS and REAC Sector Supervisor Notify APHIS and REAC Sector Supervisor of change of operation	**Content:** Institutional status (AAALAC or not) List all parts of institution to be included Describe lines of authority and responsibility List qualifications/responsibility/authority and percent of time contribution of each veterinarian IACUC membership list and procedure description Describe personnel health program Synopsis of training/instruction offered to personnel involved with animals List gross sq. ft. of each facility, species housed and average daily inventory by species
Reference	9 CFR Part 2, Subpart C 2.30	Policy IV.A.

**NOTE: PHS Policy requires compliance with AWA.*

Table 7B
Federal Reporting Requirements

	USDA Annual Report	PHS Annual Report
Submit To	APHIS, REAC Sector Supervisor (on agency form)	Through Institutional Official to OPRR
Deadline	On or before each December	At least once every 12 months
Contents	**Provide Assurance That:** Professionally acceptable standards for care, treatment and use of animals were followed Alternatives to painful protocols were considered Facilities adhere to USDA Regulations Exceptions to standards and regs. were explained by investigator and approved by IACUC **Summarize:** Exceptions to standards/regs. w/species and number of animals affected/description and explanation **State:** Location of all facilities Common name and number of animals used that: experienced no pain or distress; drugs were used to alleviate pain or distress; experienced pain or distress and drugs would have interfered with the research. Common name and number of animals being bred, conditioned or in holding not being used	**If Changes Have Occurred in Prior Year:** Report changes in program of facilities pertaining to AAALAC accreditation status Report changes in animal care/use program Report changes in IACUC membership Report date(s) IACUC conducted semiannual evaluations and submitted reports to Institutional Official **If No Changes Have Occurred in Prior Year:** State that there are no changes Report date(s) IACUC conducted semiannual evaluations and submitted reports to Institutional Official
Other	Signed or certified by CEO or Institutional Official	Include any minority views of IACUC members List USDA Facility Registration number
Reference	9 CFR Part 2, Subpart C 2.36	Policy IV.F.1. & 2.

Table 7C
Federal Reporting Requirements

	USDA Semiannual Report	PHS Semiannual Report
Submit To	Designated Institutional Official	Same as USDA
Update	Every 6 months	Same as USDA
Contents	Describe adherence to USDA Regulations	Describe adherence to *Guide* and Policy
	Identify departures from USDA Regulations	Identify departures from *Guide* and Policy
	State reasons for departure	Same as USDA
	Identify significant deficiencies	Same as USDA
	Identify minor deficiencies	Same as USDA
	Include plan/schedule to correct deficiencies	Same as USDA
	Include minority views	Same as USDA
	Not Addressed	Identify facilities accredited by AAALAC
Other	Reviewed and signed by majority of members	Must be a committee action
	Maintained by Research Facility	Maintained by institution
	Available to APHIS and funding agency upon request	Available to OPRR upon request
	Report failure to adhere to plan/ schedule through Institutional Official to APHIS and funding agency within 15 working days	No similar requirement
Reference	9 CFR Part 2, Subpart C 2.31(c)(3)	Policy IV.B.3. & IV.F.3.

Table 7D
Federal Reporting Requirements

	USDA: Suspension Report	PHS: Suspension/Noncompliance Report
Submit To	By Institutional Official with IACUC to APHIS and federal agency funding the activity	By IACUC through Institutional Official to OPRR
Submit For	Suspension of an activity by the IACUC	Same as USDA
	Not addressed	Serious deviation from the *Guide*
	Not addressed	Serious or continuing noncompliance w/Policy
Contents	Full explanation of circumstances	Same as USDA
	Description of corrective action taken	Same as USDA
	Not addressed	Minority views filed by IACUC
Reference	9 CFR Part 2, Subpart C 2.31(d)(7)	Policy IV.C.6. & 7. and IV.F.3.

Table 7E
Recordkeeping Requirements

Records	USDA Requirements	PHS Requirements
Minutes	IACUC meeting minutes w/records of attendance, activities and deliberations	Same as USDA
Protocol	Records of proposed activities using animals	Records of applications and proposals
	Record of proposed significant changes	Same as USDA
	Outcome of IACUC review	Same as USDA
Basic Documents	Semiannual IACUC reports and recommendations	Same as USDA
	Not addressed	Assurance Document
	Not addressed	Records of accrediting body determinations
Animal	Records on acquired live dogs/cats or offspring including 7 types of information	Must adhere to *Guide*
	Records on dogs/cats transported/ sold/euthanized including 3 types of information	Must adhere to *Guide*
Other Requirements	Protocol records maintained for duration of activity +3 years	Same as USDA
	Other records maintained for 3 years	Same as USDA
	Accessible to APHIS and Federal agency officials	Accessible to OPRR & other PHS officials
Reference	9 CFR Part 2, Subpart C 2.35	Policy IV.E.

tency in animal care and use components of the applications and the proposal for IACUC review.

A well-staffed IACUC greatly facilitates the efficient running of the Committee and reduces the burden on Committee members. Throughout, the staff must remember that, in addition to their primary role of the implementation of PHS Policy and USDA Regulations on behalf of their institutions, the facilitation of appropriate animal-based research is generally consistent with the institution's mission and should be encouraged.

E-3. Automated Information Systems

Introduction

The increasing responsibilities of IACUCs in receiving, monitoring and distributing information has led to such Committees' relying increasingly on automated data processing (ADP) to enhance the efficiency and accuracy of their information management systems. The potential advantages of ADP are numerous; however, it is important to consider whether the benefits actually outweigh the cost before investing extensively in equipment and software packages. To make this decision, careful analysis of the precise, and predicted, needs of the Committee is necessary.

Benefits

The use of ADP can assist the IACUC administration to improve the proposal review system, increase the efficiency in generating correspondence and reports, and enhance coordination with other institutional functions. Proposal tracking is probably the single most important function which the use of ADP may produce for the Committee.

Costs

The costs of ADP include both the purchase of the equipment and software, and the time required by IACUC staff to make the system operational. Considerable time must be allocated for planning, development and training. Additional staff may be needed to perform the new tasks associated with the ADP system.

Selecting an ADP system

The ADP system comprises hardware and software, and both must be carefully chosen to suit the tasks of the IACUC.

Hardware:
The range of options and the rapidity with which computer technology is advancing make this a difficult choice. The factors to consider include storage capacity, speed, ease of use, availability of support, and cost. Capacity and speed requirements will be determined by the amount of data to be handled, which varies considerably among IACUCs. Since upgrading is expensive and inconvenient, it is incumbent that computer needs not be underestimated.

A choice must be made whether to connect into the institution's mainframe computer to establish a local area network, or to purchase stand-alone personal computers (PCs). In the former, storage is rarely limited and information is readily accessed by other departments in the institution since only a terminal is needed. On the other hand, such computer systems are complex, tend to be fairly inflexible, and the ready access presents a security problem. The recent advances in speed and capacity of personal computers make them a desirable option, particularly for smaller IACUCs. Control is local and it is simpler to customize the system to suit the specific needs of the users.

Software:
Menu driven systems are optimal. Information is usually entered only once and is then available for a wide variety of applications. Also, different software packages should be compatible, such that information in the database can be used in word processing. Separate packages for databases, spreadsheets and wordprocessing are available, as are integrated systems which contain a number of features in one package. While software can be purchased in general-purpose packages, it will often be appropriate to develop specific applications to fulfill IACUC requirements. Some commercial packages have been developed specifically for IACUC functions, while some IACUCs may be willing to make available those which they have created. It is also possible to hire consultants to customize the software to fulfill the needs of the IACUC, but this can be expensive.

Using an ADP system

Proposal tracking and information access:
This consists of keeping track of data about individual research proposals and is best handled through a database management system. This is a system for entering data into the computer and sorting, selecting and displaying the desired information in a variety of formats as needed. The nature of the information to be stored,

the method of entering, and the ease of access of information are the key points for consideration.

Generation of reports and correspondence: This is best performed by a word processing system. Documents can be created, modified, saved and retrieved at a later date. Ideally, information can be imported directly from the database.

Coordination with other offices: The use of a mainframe allows direct access by other offices with a terminal. A PC network can achieve similar results. Alternatively, information can be exchanged by copying the information to be transferred on a disc, and carrying it to the new user. The latter is often the simplest, and adequate as long as the software is compatible among the various offices.

Training

To implement an effective system the individuals using it must understand its capabilities and uses. Training can be achieved by sending staff to external computer courses, using consultants, or requesting assistance from the institution's computer services department. One approach is to identify a particular individual on the IACUC staff familiar and/or comfortable with computers, and focus on training this person to become the reference point within the office for questions about the system.

Conclusion

An automated information management system has the potential to substantially improve the administration of the IACUC. If sufficient attention is given to analysis, planning and decision-making prior to computerization, the IACUC should be able to handle more information, more easily, with fewer staff.

F.
Special Considerations

F-1.
Numbers and Species of Animals

Numbers

To optimize the value of experiments using animals, an IACUC must consider the justification for doing the experiment at all, as well as the number of animals needed to achieve a meaningful result.

Repetition of experiments is important in certain cases. For example, changes in the available technology can greatly enhance the resolution of the data and justify a series of experiments being repeated. Also, comparisons between species are important if certain specific phenomena are to be shown to be more generally applicable. Repetition which is a direct repeat of a previous study is less readily justified and investigators are discouraged from such studies by the peer review system for proposals and publications. The USDA Regulations require that investigators state that a proposed activity is not "unnecessarily duplicative" of previous studies.

Replication within experiments can lead to a seemingly large number of animals being used; however, this may be well-justified and necessary. Biological variation in the test system can obscure the effects of a given intervention if the sample size is insufficient to obtain a statistically significant result. For this reason, it is very helpful if proposals are reviewed by a biostatistician, either before submission to the IACUC or as part of the IACUC review.

Species

Both PHS Policy and USDA Regulations require that investigators include in their proposals the rationale for selecting the species of animal to be used. Selection of species in a research proposal is largely dependent on the scientific question being asked and any pre-existing data base in the area of inquiry (including animal-based data). In general, the lowest species of animals, in phylogenetic terms, which is appropriate to answer the scientific questions, should be used. Cost considerations already encourage this. The burden for justifying the species proposed is correctly placed on the investigator with the IACUC's responsibility including evaluation of the justification, recommendation of alternative species when Committee expertise exists and assessment of the availability of the selected species. In addition, the IACUC must determine that personnel and facility resources are available to maintain the proposed species.

While inbred animals help reduce the variation within an experiment and thus the number of animals required, they necessarily reduce the generalizability of the results and may necessitate repetition of experiments with different strains.

F-2.
Alternatives to the Use of Live Animals

There is increasing public interest in alternatives to the use of animals for biological research and testing. IACUCs are being faced with the constant question, "Is there an alternative to using live animals in this proposal?" Some suggest that the only acceptable alternatives are those which completely replace animals, while others have less restrictive definitions. The definition of alternatives which allows a degree of common understanding was originally developed by Russell and Burch, and is defined as the three "Rs"—replacement, refinement, or reduction—as acceptable alternatives. For this discussion, the term alternatives refers to systems which do not employ whole live animals.

Alternatives to the use of animals include *in vitro* model systems. For example, isolated organ preparations such as the perfused heart, represent *in vitro* models. More commonly, *in vitro* systems are thought of as cell, tissue and organ cultures. The source of the tissue may be primary tissue or cell lines, obtained invasively or non-invasively. Tests have been developed using *in vitro* systems, for the evaluation of cytotoxicity, inflammation, genotoxicity, and target organ toxicity among others. A third alternative is the use of non-biological models systems. These include chemically-based systems, physical models such as hemodynamic flow chambers or computer simulations. The quality of these systems is limited by the biological databases already available. More mechanistic models are being developed, such as quantitative structure-activity responses, linear modeling relationships, and three dimensional computation models. As more data become available, an expansion in this area can be anticipated.

Refinement and reduction alternatives are discussed in other chapters of this Guidebook.

Resource Organizations for Alternatives

Animal Welfare Information Center (AWIC)
National Agricultural Library, Room 304
Beltsville, MD 20705
(301) 504-6212 FAX (301) 504-5472

Institute for Laboratory Animal Resources (ILAR)
National Research Council
2101 Constitution Avenue, N.W.
Washington, DC 20418
(202) 334-2590 FAX (202) 334-1639

Johns Hopkins Center for Alternatives to Animal Testing (CAAT)
615 North Wolfe Street
Baltimore, MD 21205
(410) 955-3343 FAX (410) 955-0258

National Institutes of Health
National Library of Medicine
Bethesda, MD 20894
(301) 496-6095 FAX (301) 496-4450

Public Responsibility in Medicine and Research (PRIM&R)
132 Boylston Street, 4th Floor
Boston, MA 02116
(617) 423-4112 FAX (617) 423-1185

Scientists Center for Animal Welfare (SCAW)
Golden Triangle Building One
7833 Walker Drive, Suite 340
Greenbelt, MD 20770
(301) 345-3500 FAX (301) 345-3503

F-3. Instructional Use of Animals

Introduction

Any instructional use of animals supported by PHS funds is governed by PHS Policy. The applicability of the USDA Regulations depends upon the species to be used. Most institutions have chosen to require that all instructional use of animals, regardless of funding source or species, be reviewed by the IACUC.

It may be appropriate for students, at both undergraduate and graduate levels, to participate in the conduct of experiments involving animals for the purpose of education. All instructional proposals should clearly justify the particular value of animal use as part of the course, whether it is demonstration of a known phenomenon; acquisition of practical skills; or exposure to research.

In all cases, consideration must be given to alternative approaches to attaining the desired educational objectives, keeping in mind the U.S. Government Principles. A key role of the IACUC is to ensure that maximum effort is made to avoid pain and distress. Studies involving unrelieved painful procedures are generally unsuitable for purely teaching purposes (U.S. Government Principle IX).

Adequate supervision and training are especially important as the techniques learned by students are those which will be carried into subsequent research careers. It is recommended that students receive instruction on the ethics of animal research prior to undertaking any experimentation. When students work within an investigator's laboratory rather than take a course covering the use of animals in research, the IACUC must assure that the students receive appropriate supervision and training in animal care and use. Student projects involving protocols different from those approved for the instructor's laboratory must be reviewed and approved on their own merits by the IACUC.

Experiments often entail behavioral observation with no intervention, or minor non-painful interventions, such as choices of food or living accommodations. Such projects teach the rigors of conducting a research project and the variability inherent in animal research. These exercises generally involve little or no distress to the animals.

Some procedures present additional concerns. Selected examples are listed below:

Behavioral studies that involve conditioning procedures in which animals are trained to perform tasks using non-aversive stimuli or mildly aversive ones, such as the noise of a buzzer, may be potentially stressful to the animals. For other behavioral studies, such as running mazes, it may be necessary to maintain animals at a reduced body weight to enable food treats to be used as an effective reward. Experiments involving food and water deprivation are potentially stressful and must be rigorously justified for teaching purposes.

Some behavioral studies produce potentially high levels of distress, including those using aversive stimuli, such as unavoidable electric shock, and surgical ablations or drug-induced lesions designed to affect the animal's behavior or performance. The educational benefits of such procedures should be carefully reviewed and clearly justified, bearing in mind that studies involving unrelieved pain or distress are generally inappropriate when employed solely for instructional purposes (U.S. Government Principle IX).

Laboratory experiments in physiology, neurophysiology, biology and pharmacology often involve observations and experiments using animals. For all procedures, including those in which animals are euthanized to obtain tissues, e.g., in the teaching of anatomy or tissue harvest for *in vitro* procedures, the method of euthanasia and tissue harvest protocols must be reviewed by the IACUC. The number of animals used should be the minimum necessary to accomplish the objectives of the proposed educational activity.

Animal use in veterinary surgery laboratories

Most North American veterinary schools use live animals to teach anesthesia, animal handling, surgical procedures, recovery from anesthesia, postoperative management and postmortem examinations following terminal procedures. Requiring that all instructional use of animals be made non-survival would greatly increase the number of animals used and the expense of instruction, but all such exercises should be reviewed and federal prohibitions against multiple survival surgeries observed. Cost savings alone is not an adequate reason for performing multiple survival surgical procedures.

Alternatives to the use of animals acquired specifically for such instruction include the use of client-owned animals, or dogs and cats from humane societies which are made available for surgical neutering. Some states have specific laws forbidding the latter. Plastic models, and other model systems, are increasingly being use to teach manipulative skills.

Many pet owners whose animals develop unique and/or terminal conditions will suggest donating their pet to a veterinary school for care and or teaching purposes. The use of these animals needs full IACUC review.

Animal use in agricultural instruction

Flocks and herds of agricultural animals are often maintained by agricultural schools to teach husbandry, production, and showmanship. Technically, food and fiber animals used in such practices are not covered by PHS Policy or USDA Regulations. However, any invasive procedure, e.g., i*n vitro* fertilization, warrants committee review and institutions often choose to treat all agricultural animal use according to the PHS Policy.

IACUCs charged with reviewing the use of animals in activities with agricultural applications will find *A Guide for the Care and Use of Agricultural Animals in Agriculture Research and Teaching* useful in conducting their evaluation.

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F-4.
Farm Animals

Introduction

Monitoring research and teaching activities using agricultural animals often requires that an IACUC deal with the routine problems and ethical dilemmas of animal use and with agricultural traditions and the complicated administrative structures found in some colleges of Agriculture. The PHS Policy and USDA Regulations cover biomedical research but not food and fiber research. However, the welfare concerns should not differ between the two groups.

One major goal of agricultural research is to reduce the labor required for food and fiber production, and thus increase the efficiency of production. Many of the means of increased production also place restrictions on the activity and behavior of the animals. Many of the ethical questions surrounding current agricultural practices center on the economic, bioethical and environmental costs and benefits of using technology to manipulate plant and animal life for human purposes.

Monitoring agricultural animal care and use

In order to be relevant to commercial production, agricultural research is often conducted under conditions which are feasible and appropriate to farmers, and which incorporate economic considerations. There are practices which are common in commercial agriculture which would not be permitted under the regulations governing biomedical research, for example, the castration of young animals without anesthesia.

Standards for evaluation of animal research and teaching

Food and fiber research and teaching activities are not covered by USDA Regulations or PHS Policy. A consortium of scientific and professional organizations, industrial groups, and government agencies has developed a *Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching (Agri Guide).* It was prepared based on the *Guide,* but is directed specifically towards agricultural research activities with special consideration of current practices and issues in commercial agriculture.

The *Agri Guide* specifies that the IACUC should include: "a scientist from the institution with experience in agricultural research or teaching involving agricultural animals; an animal scientist with appropriate training and experience in the management of agricultural animals and with recognized high professional credentials as verified by the scientific and professional societies in animal science, dairy science, or poultry science; a veterinarian who has appropriate training and experience in agricultural animal medicine and who is appropriately licensed or eligible to be licensed to practice veterinary medicine; a non-scientist affiliated with the institution; a person not otherwise affiliated with the institution; other members as required by institutional needs and applicable laws, regulations and policies."

The IACUC should meet regularly and review all animal use practices at the institution. The adoption of the *Agri Guide* is voluntary but the American Association for the Accreditation of Laboratory Animal Care (AAALAC) has approved portions of the *Agri Guide* as the basis for accreditation of agricultural animal programs. OPRR encourages its use as a reference, as well, for IACUCs reviewing proposals for both biomedical and agricultural research involving farm animal species.

Clearly defined administrative authority for the animal care program is necessary. The absence of species-specific standards for the maintenance of agricultural species used in biomedical research can present difficulties for the USDA- or PHS-mandated IACUC. Consequently, at institutions with large agricultural research programs it may be prudent to establish more than one IACUC, each with separate responsibilities.

Proposal review and facility inspection

A consistent system of proposal review is essential, but it is sometimes unclear whether a proposal falls under the provisions of PHS Policy or simply the *Agri Guide.* There are some activities involving agricultural animals which may not necessitate IACUC review, for example, public education extension activities. The IACUC should be aware that good animal care can proceed despite modest facilities, but investigators should not use tradition as a defense for inadequate care.

Conclusion

Although not currently required by law, the monitoring of food and fiber animal research and teaching activities can significantly benefit an institution by improving the overall quality of the animal care program.

Food and fiber animal research is often conducted under conditions which mimic farm conditions. Because of this difference, review of proposals which have food or fiber production as an endpoint, sometimes differ from those for laboratory animals. However, this does not mean that different ethical standards should be used by an IACUC in considering the use of these animals

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F-5. Legal Concerns

IACUCs are usually created in response to federal law and institutional policies. Hence, Committee members must be made aware of the legal obligations of their institutions, the responsibilities of the Committees, and the regulatory requirements for which they may be personally accountable.

Rights and obligations of IACUC members

Committee members must be cognizant of federal and state laws and regulations, as well as the interpretations of the regulations by the primary agencies.

- The Committee should be familiar with any institutional committee charter, the institution's Animal Welfare Assurance with OPRR, and any other guidelines or operating directives which impact their authority.
- Any member may request that the IACUC Chairman or the institution's counsel obtain a legal opinion to help guide the Committee's actions if there is any doubt about the legal ramifications of an issue before the panel.

Liability—Who is Responsible for What?

The primary responsibility for meeting applicable state and federal standards rests with the registered research facility or PHS awardee institution. The Administrator of APHIS, USDA is responsible for enforcing the Animal Welfare Act through its regulations. Under applicable statutory provisions (7 U.S.C. Section 2149), USDA has the authority to suspend a facility's registration for failure to comply with the regulatory and statutory requirements and to impose a fine. OPRR has the authority to withdraw approval of an institution's Animal Welfare Assurance, thereby requiring PHS Awards (e.g., NIH Grants) to be immediately discontinued (an approved Assurance is a prerequisite for receipt of PHS Awards).

While there are many requirements assigned to the IACUC by the statutes and rules, they do not create specific penalties for violations by the Committee. Liability is unlikely to be an issue unless flagrant violations focus attention on the Committee or individual members.

To what extent must information be public?

A topic which has become the focus of litigation and public attention is the extent to which the public should have access to information reviewed and generated by IACUCs in states in which "sunshine laws" are in place. Suits have been successfully initiated against institutions in which IACUCs have met in closed sessions. State sunshine laws vary greatly but most require that meetings of decision-making committees at government-supported institutions be open to the public. OPRR has interpreted PHS Policy to make the IACUC an advisory, as opposed to dispositive, committee. This distinction has allowed IACUCs in some states to continue to hold closed sessions.

In addition, a Committee member should be aware of FOIA, which requires that the Department of Agriculture must provide copies of information, which it holds in the conduct of its business, to a member of the public who requests such data. This includes information which agencies, such as the USDA, obtain from regulated research institutions.

Committee members must be sensitive to the need to balance the public's right to know, and the institution's need to protect, proprietary information. Any information submitted to the Committee may be subject to review by the Agency and ultimately available to requests from the public. Animal procedure statements, minutes of the Committee meetings and the annual report of the institution are among the items which may be demanded by the public domain.

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G.
Resources

American Association for the Accreditation of Laboratory Animal Care (AAALAC)
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American Association for Laboratory Animal Science (AALAS)
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American College of Laboratory Animal Medicine (ACLAM)
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Division of Comparative Medicine
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American Society of Laboratory Animal Practitioners (ASLAP)
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Applied Research Ethics National Association (ARENA)
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Boston, MA 02116
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Center for Alternatives to Animal Testing (CAAT)
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National Association for Biomedical Research (NABR), and Foundation for Biomedical Research (FBR)
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Washington, DC 20006
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Phone: 202/457-0654 FAX: 202/457-0659 (FBR)

National Library of Medicine (NLM)
8600 Rockville Pike
Bethesda, MD 20894
Phone: 1-800/272-4787 FAX: 301/496-2809

Office for Protection from Research Risks (OPRR)
Division of Animal Welfare
National Institutes of Health
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Scientists Center for Animal Welfare (SCAW)
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H.
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